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Acid-Catalyzed Reactions of 1,2-*O*-[1-(*exo*-Ethoxy)Ethylidene]-3,4,6-tri-*O*-Methyl-β-D-Mannopyranose with Ethanol

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ACID-CATALYZED REACTIONS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE WITH ETHANOL

A thesis submitted by

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SUMMARY

Acid-catalyzed ethanolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose [a mannose 1,2-(ethyl orthoacetate)] at 25.0°C were analyzed by GLC, NMR, and polarimetry. Initially, a 27% endo-ethoxy isomer-73% exo-ethoxy isomer equilibrium mixture of the orthoester was formed. In slower, parallel first-order reactions, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (and ethyl acetate), and 3,4,6-tri-O-methyl-D-mannopyranose (and triethyl orthoacetate) were formed from the mannose 1,2-(ethyl orthoacetate). In the presence of lithium p-toluenesulfonate, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside and ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside were also formed. Deviation from parallel first-order kinetics was noticed after 60% of the mannose 1,2-(ethyl orthoacetate) had disappeared. This was caused by secondary reactions of 3,4,6-tri-O-methyl-D-mannopyranose with triethyl orthoacetate to form intermediate carbohydrate orthoesters which subsequently underwent ethanolysis to yield mannopyranosides.

Ethanolyses of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate at 25.0°C were followed by GLC analysis of the carbohydrates. Ethyl 3,4,6-tri-O-methyl-α- and β-D-mannopyranoside and 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose were formed in parallel reactions. The parallel reactions exhibited first-order kinetic dependence on both the reducing sugar and the triethyl orthoacetate. The mannose 1,2-(ethyl orthoacetate) was not a stable product and underwent ethanolysis reaction described above.

A kinetic model was developed for the ethanolysis. Computer simulations using the kinetic model (with experimentally determined rate constants) were in excellent agreement with the experimental results.

Decreasing the ethanol concentration of reactions run at 40°C increased glycoside formation relative to reducing sugar formation, increased 2-O-acetyl-glycoside formation relative to 2-hydroxyglycoside formation, and decreased the stereoselectivity of the reaction for formation of α-mannopyranosides. Decreasing the solvent polarity (at a constant ethanol concentration) increased the formation of 2-O-acetyl-glycosides relative to 2-hydroxyglycosides.

Mechanisms for the reactions of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose are proposed. The dominant mechanism for exo-endo isomerization apparently involves the 1,2-acetoxonium ion. The mechanisms proposed for glycoside formation involve formation of a carbonium ion at C-1 of the sugar concurrently with formation of a diester of an orthoacid. This can occur as either (1) the initial step or (2) subsequent to a trans-ortho-esterification to form a 1-O-(1,1-diethoxyethyl) group. Ethanol reacts at the C-1 carbonium ion to form α- and β-mannopyranosides and the diester of the orthoacid forms an ester and an alcohol. The 1,2-acetoxonium ion cannot be rigorously excluded as an intermediate leading to glycoside formation. However, all the experimental results can be readily explained without invoking this intermediate for glycoside formation. The two mechanisms proposed for formation of the reducing sugar and triethyl orthoacetate involve two successive trans-orthoesterification steps in which only the order of bond cleavage is different.

One of the proposed mechanisms for glycoside formation involves a 2-O-(1-ethoxy-1-hydroxyethyl) substituted intermediate. A study of the acid-catalyzed hydrolysis of ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside demonstrated that both 2-hydroxy and 2-O-acetyl derivatives could be generated from a 2-O-(1-ethoxy-1-hydroxyethyl) substituted intermediate.

The acid-catalyzed hydrolyses yielded ethyl 3,4,6-tri-O-methyl-α-D-manno-pyranoside and its acetylated analog, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside. As in the case of reactions of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, decreasing the solvent polarity increased the formation of the 2-O-acetyl-glycoside relative to the 2-hydroxy-glycoside.

INTRODUCTION

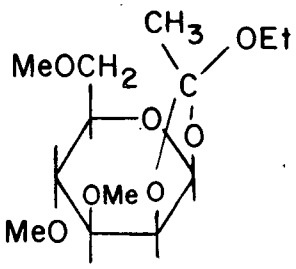
GENERAL

The search for stereospecific, high-yield syntheses of glycosides and oligosaccharides is one of the classical topics of carbohydrate chemistry. Access to such syntheses would be of considerable interest in both natural products and biological chemistry.

One of the newer and most successful methods of producing 1,2-*trans*-glycosides (including oligosaccharides) is the acid-catalyzed reaction of glycose 1,2-(alkyl orthoacylates) with alcohols (1-6). The so-called ortho-ester method of glycosylation (reaction of orthoesters with alcohols in inert solvents) is generally stereoselective, giving 1,2-*trans*-2-*O*-acyl-glycosides (3), although undesired side products have been noted (4,7-11).

This thesis was undertaken to provide a more complete understanding of the mechanisms of reactions of glycose 1,2-(alkyl orthoacylates) with alcohols. Such an understanding would allow the selection of reaction conditions most favorable for the formation of the desired glycoside (or oligosaccharide), and minimize the formation of undesirable products.

Orthoesters have three ether linkages to a single carbon atom, which is sometimes referred to as the orthoester carbon. In carbohydrate orthoesters, one or more of these ether linkages are attached to a carbohydrate molecule. An example of a glycose 1,2-(alkyl orthoacylate) is 1,2-*O*-[1-(*exo*-ethoxy)-ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose.



1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose

Two diastereomers are possible for 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose. In agreement with the literature (12-14), in this thesis, the exo-ethoxy stereochemistry was assigned to the isomer which has the orthoacetyl methyl singlet at the lower NMR field position. Although both isomers may be discerned by NMR, the assignment of configuration on this basis is not necessarily absolute. However, this does not change the validity of the conclusions.

The orthoester group on sugars is generally stable in alkaline media, and because of this stability, orthoesters are useful as blocking groups in synthetic work (1,4-5,15-18). Perhaps the most important use of sugar orthoesters, however, is their use as intermediates in glycoside (including oligo- and polysaccharide) syntheses.

Glycoside syntheses from glycose 1,2-(alkyl orthoacylates) fall into two groups which differ considerably in both product distributions and conditions. These are (1) reaction with alcohol in an inert solvent and (2) alcoholysis.

REACTIONS WITH ALCOHOLS IN INERT SOLVENTS

Kochetkov, et al. (2) found that acid-catalyzed reactions of glycose 1,2-(alkyl orthoacylates) with alcohols in refluxing nitromethane was a "stereospecific" route to 1,2-trans-2-O-acyl-glycosides. Although no detailed

mechanistic studies were made, the mechanism given in Fig. 1 was suggested for the reaction.

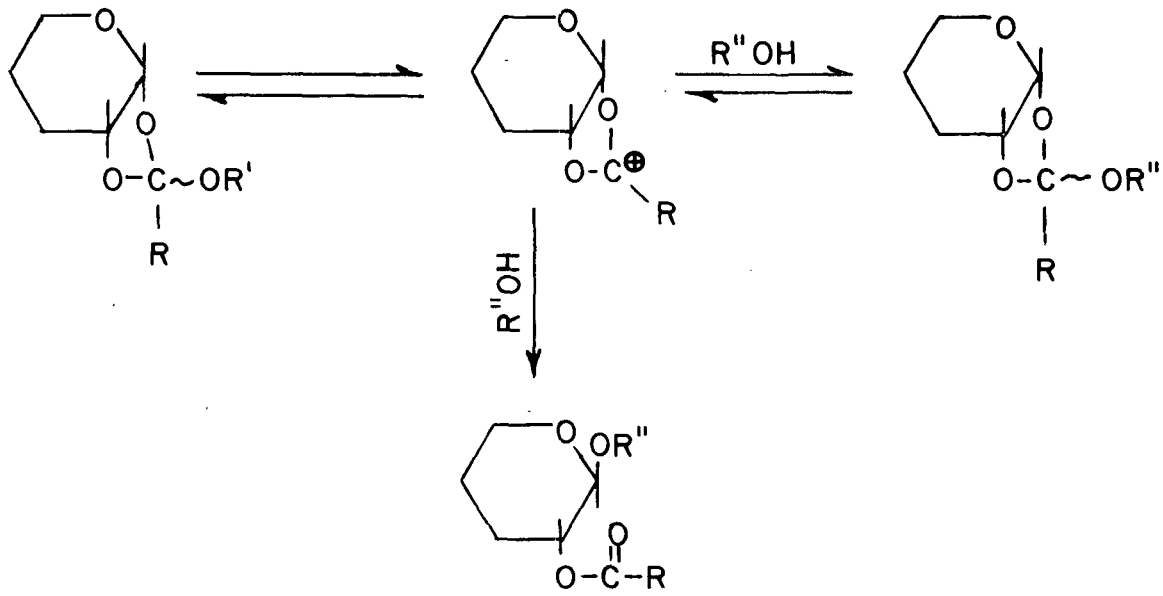


Figure 1. Mechanism Proposed by Kochetkov and Coworkers (2) for Acid-Catalyzed Reactions of Glycose 1,2-(Alkyl Orthoacylates) with Alcohols (Nonparticipating Ring Substituents Omitted)

Additional work has confirmed the generality of the orthoester method of glycosylation (3-11), but several observed products are not accounted for by the mechanism shown in Fig. 1. These products are 1,2-*trans*-2-hydroxyglycosides (4,7,10), 1,2-*cis*-glycosides (7-9), and acetates of the alcohols (11).

Obviously, the orthoester method of glycosylation involves more than the mechanism shown in Fig. 1, and because of the utility of orthoesters as intermediates in glycoside syntheses, a better understanding of the mechanism(s) involved is desirable.

ALCOHOLYSES

In alcoholyses, the alcohol serves as both a reactant and a solvent. A survey (1,19) of alcoholyses of glycose 1,2-(alkyl orthoacylates) indicates that the following carbohydrate products have been detected: 1,2-trans-2-O-acyl-glycoside, 1,2-cis-2-O-acyl-glycoside, 1,2-trans-2-hydroxyglycoside, 1,2-cis-2-hydroxyglycoside, and 2-hydroxyglycose. In addition, alkyl acylates and 1,1,1-trialkoxy alkanes, derived from the orthoester moiety, have been found (1).

The two most detailed studies of alcoholyses of glycose 1,2-(alkyl orthoacylates) were made by Hultman (1) and Perlin (20). Hultman (1) studied the acid-catalyzed ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose. Initially, ethanolysis resulted in rapid formation of a 20% endo-ethoxy-80% exo-ethoxy equilibrium mixture. In slower, parallel first-order reactions, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside, ethyl 3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside, and 3,4,6-tri-O-methyl-α-D-glucopyranose were formed. Deviations from parallel first-order kinetics were noticed after 70% of the 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose had disappeared. This was caused by a slow reaction of 3,4,6-tri-O-methyl-D-glucopyranose with triethyl orthoacetate, which was also a product of the reaction, to form intermediate carbohydrate orthoesters which subsequently underwent ethanolysis to yield glucopyranosides.

Perlin (20) studied the acid-catalyzed methanolyses of both a glucopyranose orthoester and of a mannopyranose orthoester. The acid-catalyzed methanolysis of 3,4,6-tri-O-acetyl-1,2-O-(1-ethoxyethylidene)-α-D-glucopyranose yielded 3,4,6-tri-O-acetyl-D-glucopyranose and methyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside in nearly equal amounts; the acid-catalyzed methanolysis of 3,4,6-tri-O-acetyl-1,2-O-(1-methoxyethylidene)-β-D-mannopyranose yielded

3,4,6-tri-O-acetyl-D-mannopyranose (80%) and a small portion of an anomeric mixture of methyl D-mannopyranosides. In addition, the first-order polarimetric rate constant for the acid-catalyzed methanolysis of the glucopyranose orthoester was approximately twice that for the methanolysis of the mannopyranose orthoester.

Hultman (1), on the basis of a very detailed study, proposed mechanisms for acid-catalyzed ethanolyses of 1,2-O-[1-(exo-alkoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranoses. This thesis was undertaken to further test the generality of these mechanisms. A mannose 1,2-(alkyl orthoacylate), 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose, was selected as the reactant because a less comprehensive study (20) indicated that there are significant differences between the alcoholyses of glucose and mannose 1,2-(alkyl orthoacylates).

RESULTS

ACID-CATALYZED ETHANOLYSES

The reaction scheme shown in Fig. 2 represents the reactions involved in acid-catalyzed ethanolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. Initially, ethanolysis resulted in formation of a 27% endo-ethoxy-73% exo-ethoxy equilibrium mixture. In slower, parallel first-order reactions, glycosides and reducing sugar were formed. Deviation from parallel first-order kinetics was noticed after 60% of the 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose had disappeared. This was caused by a slow reaction of the reducing sugar with triethyl orthoacetate, which was also a product of the reaction, to form intermediate carbohydrate orthoesters which subsequently underwent ethanolysis to yield glycosides. This description results from studies of the reaction by quantitative gas-liquid chromatographic (GLC) procedures, polarimetry, and nuclear magnetic resonance spectrometry (NMR).

EXO-ENDO ISOMERIZATION

Ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose initially resulted in the formation of an equilibrium mixture of both isomers of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, and the isomerization was fast relative to loss of the 1-ethoxyethylidene group. Since exo-endo isomerization is a relatively fast reaction, a weak acid catalyst (2,6-dichlorobenzoic acid) was used so that the reaction could be conveniently studied. Polarimetric results were consistent with a rapid reaction followed by a slower reaction. NMR analysis showed that the rapid reaction was, in fact, exo-endo isomerization.

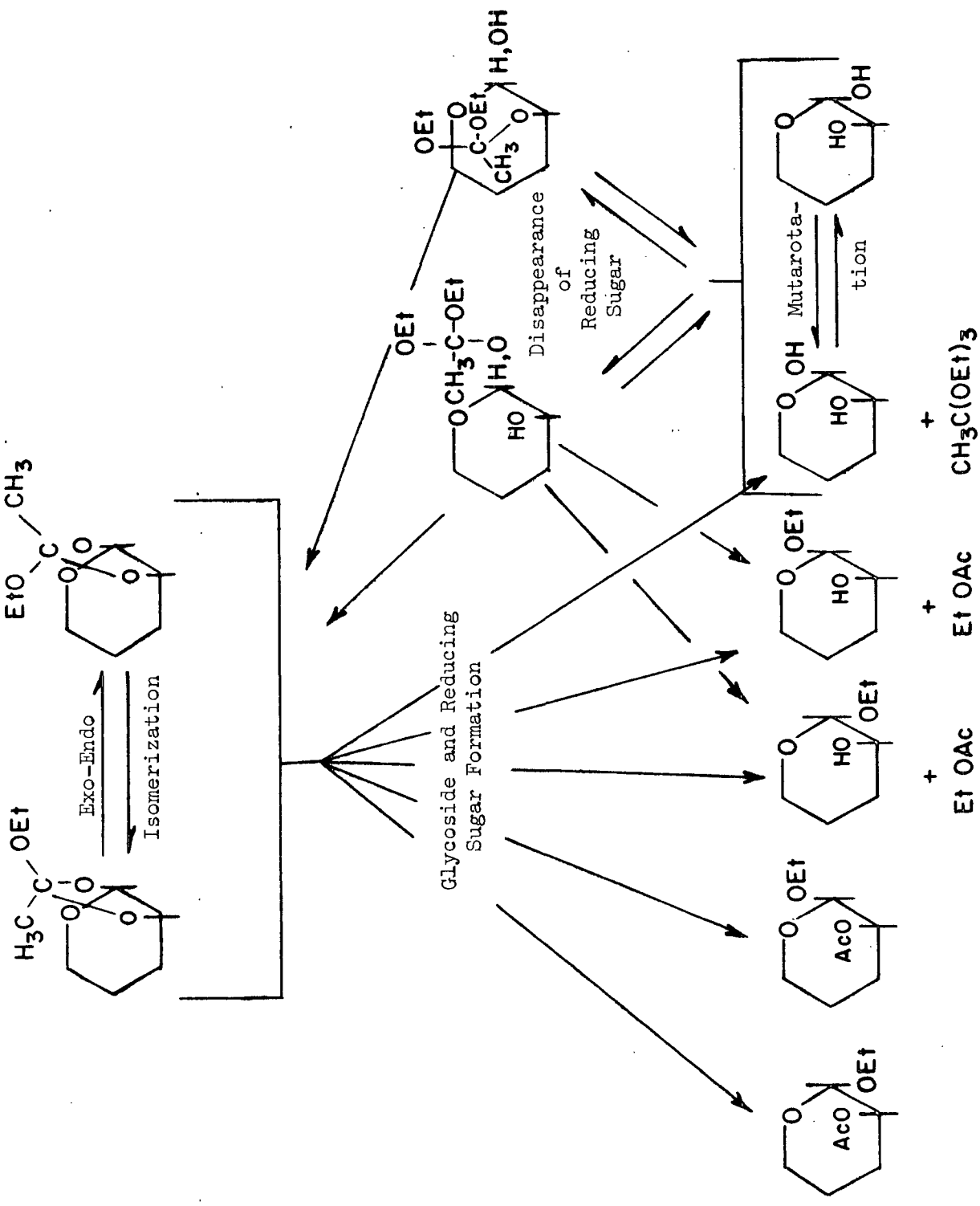


Figure 2. Reactions Occurring in Acid-Catalyzed Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. (The 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

Polarimetric Analysis

The acid-catalyzed (0.00526N 2,6-dichlorobenzoic acid) ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose exhibited a minimum in the molar specific rotation[1]-vs.-time curve (see Fig. 3). This minimum occurred at a time corresponding to about 17% disappearance of mannose orthoester and suggests a rapid reaction followed by a slower reaction. Although a minimum in the molar specific rotation-vs.-time curve was not found in picric acid-catalyzed ethanolysis, a minimum point must exist since the initial optical rotation readings (at 1-2 min from time zero) were significantly lower than that expected for the starting material (see Appendix I, Tables XI, XII, and XIV). The reaction was apparently too fast to detect the minimum.

Nuclear Magnetic Resonance Spectrometry

The initial portion (up to ca. 30% disappearance of 1,2-orthoesters) of the acid-catalyzed (0.00528N 2,6-dichlorobenzoic acid) ethanolysis was analyzed by a procedure utilizing NMR. Isomeric ratios were calculated from the NMR integrals of their respective orthoacetyl methyl singlets: exo-ethoxy, $\delta \approx 1.72$ ppm; endo-ethoxy, $\delta \approx 1.53$ ppm ($CDCl_3$). The data are presented in Table I, and portions of two spectra ($0.0 \leq \delta \leq 2.0$ ppm) are reproduced in Fig. 4. The equilibrium mixture that was established consisted of approximately 27% of the endo-ethoxy isomer and 73% of the exo-ethoxy isomer. The pseudo first-order rate constants found were $k_{exo \rightarrow endo} = 0.40 \times 10^{-4}$ sec^{-1} and $k_{endo \rightarrow exo} = 1.1 \times 10^{-4}$ sec^{-1} (see Appendix II).

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[1]Molar specific rotation, $\alpha_m(t)$ is defined by the following equation:

$$\alpha_m(t) = \frac{\alpha(t) \times 10}{\ell \cdot M_o}, \qquad (1)$$

where $\alpha(t)$ = the experimentally measured rotation at time t using 546-nm light,
ℓ = pathlength through the sample in decimeters, and
M_o = initial concentration of the reactant, moles/liter.

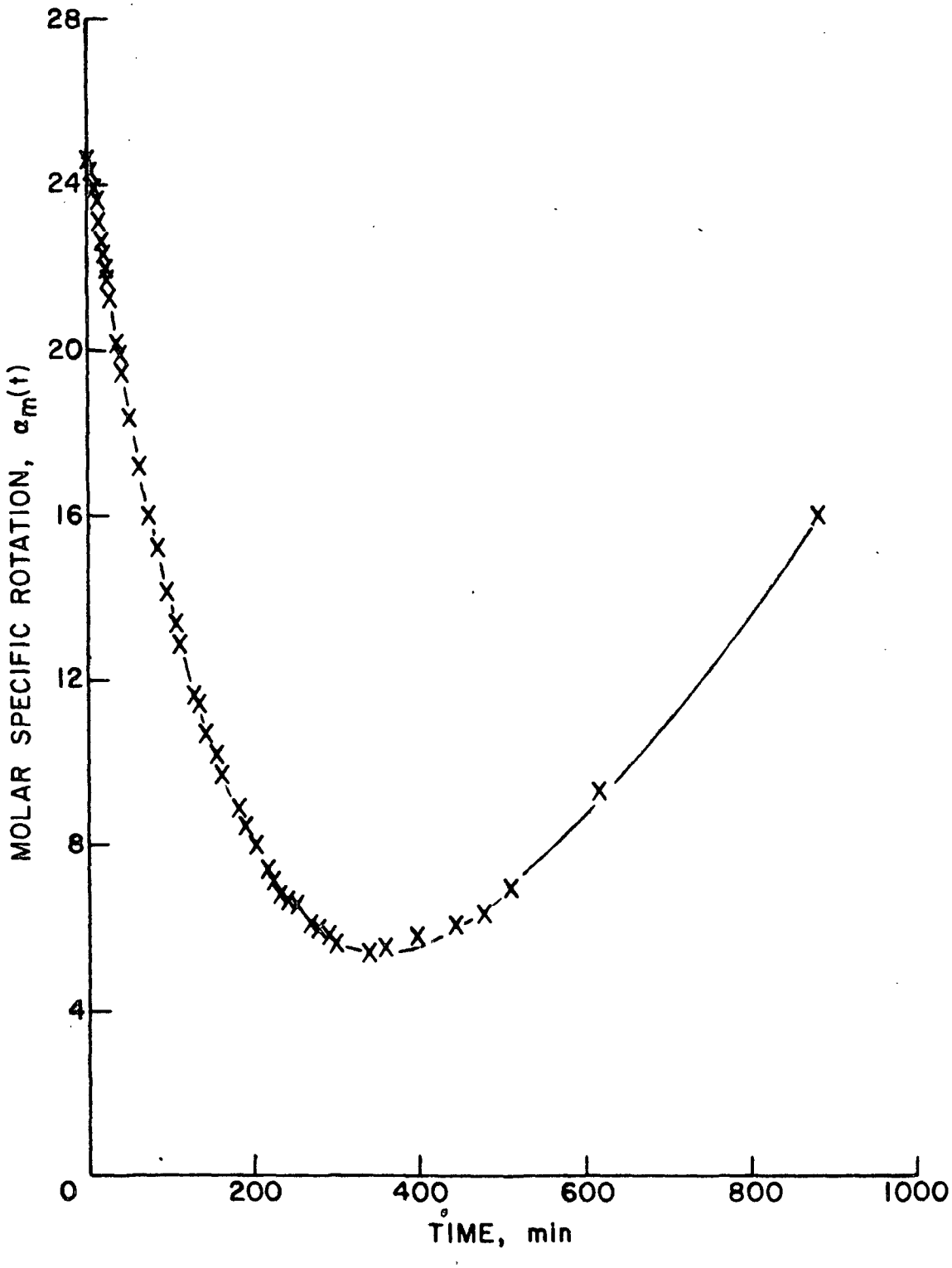


Figure 3. Polarimetric Data. Acid-Catalyzed (0.00528N 2,6-Dichlorobenzoic Acid) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C

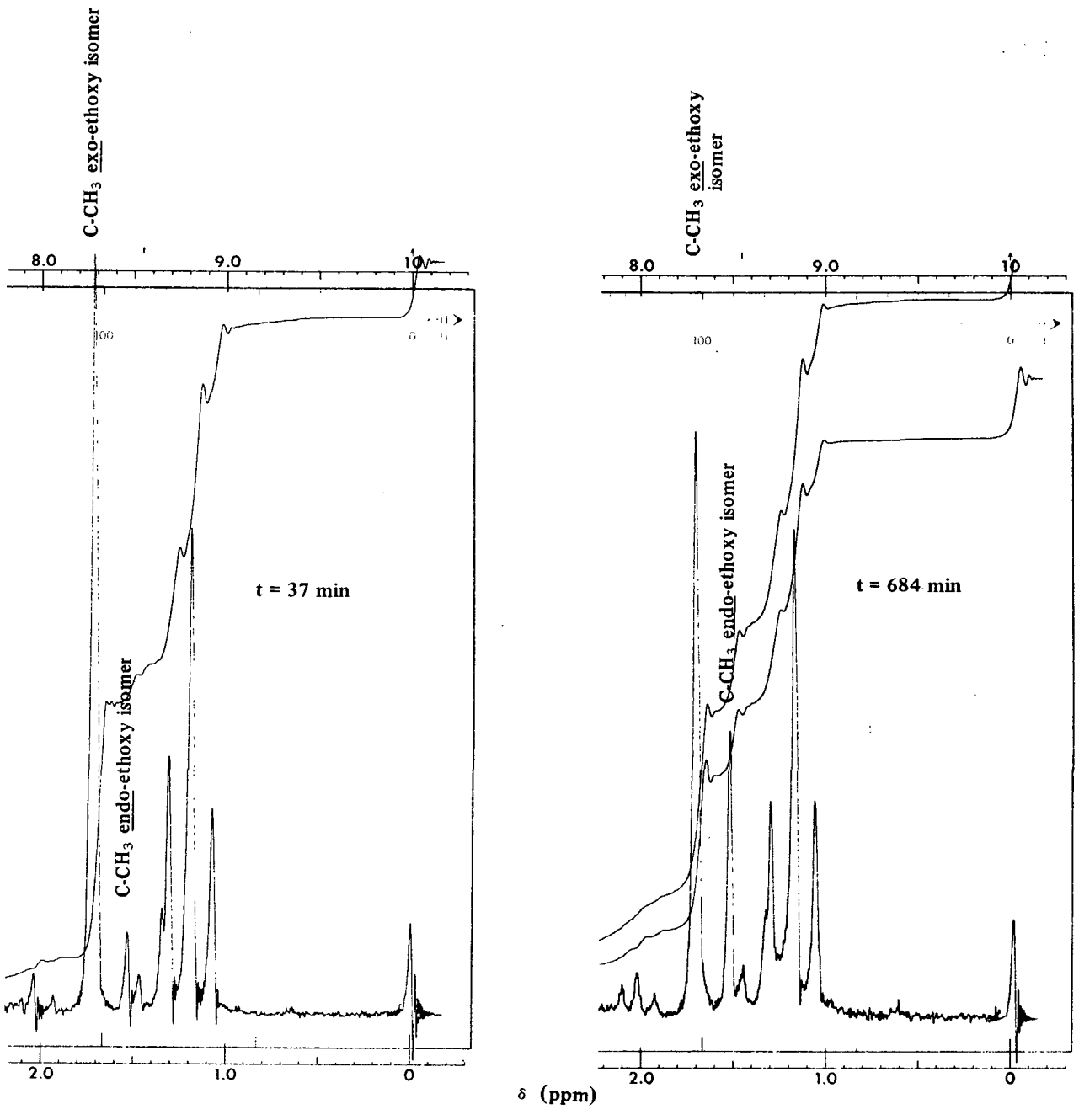


Figure 4. Partial NMR Spectra Showing Exo-Endo Isomerization for the Acid-Catalyzed (0.00528N 2,6-Dichlorobenzoic Acid) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C

TABLE I

EXO-ENDO ISOMERIZATION OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] IN 25°C ETHANOLIC 0.00528N 2,6-DICHLOROBENZOIC ACID

Time, min	Normalized Mole Fraction	
	Exo-ethoxy Isomer	Endo-ethoxy Isomer
37	0.92	0.08
170	0.79	0.21
411	0.74	0.26
684	0.73	0.27

[a] 0.0713M.

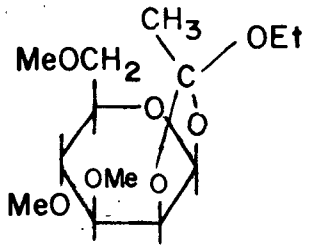
FORMATION OF GLYCOSIDES AND REDUCING SUGAR

Ethanolyses of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose[2] were followed by analysis of the reactant and the products. Identification and quantitative analyses (as a function of time) of the glycosides and reducing sugar were made by GLC. Polarimetric data indicated that the β-anomer of the reducing sugar was formed initially in ethanolysis. Triethyl orthoacetate and ethyl acetate, which were generated from the 1-ethoxyethylidene group, were identified by NMR, and quantitative analyses of the sum of the mole fractions of these two products were obtained by GLC.

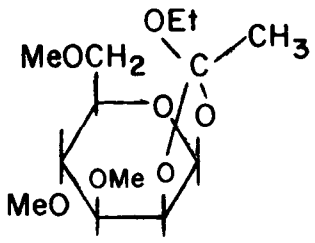
[2] Since exo-endo isomerization was fast relative to mannose orthoester disappearance, an exo-endo equilibrium mixture of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose was established in the early stages of ethanolyses.

Carbohydrate Analysis

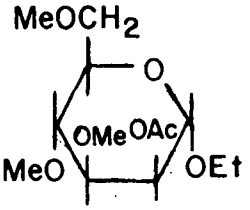
The measurable carbohydrate products resulting from the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I) were: ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside (II), ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (IV), ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (V), and 3,4,6-tri-O-methyl-D-mannopyranose (VI). A measurable amount of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside (III) was formed only in an ethanolysis with lithium p-toluenesulfonate present. These products were identified by comparison of GLC retention times with synthesized, authentic samples (see Experimental), and are the expected products, based on the literature (1).



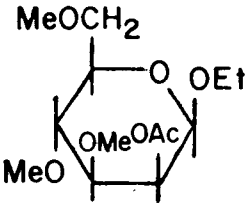
I-exo



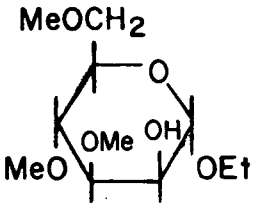
I-endo



II



III



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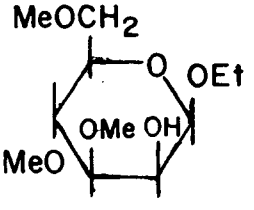
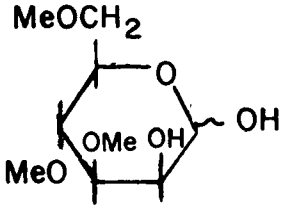


V



VI

Data in Table II illustrate carbohydrate products and reactant analyses as a function of time for a 0.005N picric acid-catalyzed ethanolysis at 25.0°C. As indicated in Table II, the measured carbohydrates gave an acceptable mole balance based on the original reactant. The carbohydrate analysis data for additional ethanolyses are given in Appendix III, Tables XV-XVII. The mole fractions shown in these tables were obtained using the appropriate response factors and equations given in Appendix IV.

The initial carbohydrate products of the reaction were 3,4,6-tri-O-methyl-D-mannopyranose, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside. After an induction period (ca. 10 min), ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside was detected. 3,4,6-Tri-O-methyl-D-mannopyranose reached a maximum concentration at ca. 25 min, then decreased.

In a control experiment, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside did not react after 42 hr [ca. 315 half-lives of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose] at 25.0°C in ethanolic 0.00525N picric acid. Thus, acid-catalyzed transacetylation and transglycosylation of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside were unimportant in ethanolysis.

Kinetics

The disappearance of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I) and appearance of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside, and 3,4,6-tri-O-methyl-D-mannopyranose were adequately described by parallel first-order kinetics initially (up to ca. 60% reaction of I).

TABLE II

ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00512N PICRIC ACID

Time, min	Mole Fraction[b] Products				Reactant Orthoester	Total Measured
	α Et 2-O-Ac[c]	α Et[d]	β Et[e]	TMM[f]		
2.5	0.051 (6)	0.038 (3)	0.000 (0)	0.158 (5)	0.742(31)	0.990(39)
3.3	0.064 (3)	0.053 (6)	0.000 (0)	0.209 (8)	0.689 (8)	1.015(23)
4.2	0.073(11)	0.060 (6)	0.000 (0)	0.242 (4)	0.639(14)	1.013(28)
6.0	0.093 (4)	0.076 (9)	0.000 (0)	0.297 (5)	0.568 (9)	1.033(14)
10.0	0.107(11)	0.094 (9)	0.002 (2)	0.391(11)	0.415(17)	1.009(45)
19.8	0.163 (8)	0.156 (6)	0.014 (2)	0.479 (9)	0.221(15)	1.032(22)
25.4	0.169 (7)	0.179(13)	0.019 (3)	0.496 (4)	0.167 (4)	1.028(18)
30.3	0.187(17)	0.189 (7)	0.021 (2)	0.455(16)	0.123 (7)	0.976(48)
61.0	0.201(11)	0.256 (4)	0.046 (3)	0.454(15)	0.054 (8)	1.011(23)
89.9	0.224(14)	0.299(12)	0.060 (6)	0.377(14)	0.031 (5)	0.991(48)
119.9	0.222(14)	0.325(14)	0.066 (7)	0.339 (5)	0.020 (8)	0.973(29)
182.5	0.252 (4)	0.392(10)	0.087 (3)	0.286 (3)	0.012 (8)	1.029 (6)
251.2	0.250 (2)	0.399(24)	0.094 (1)	0.229(14)	0.008 (3)	0.980(32)
340.6	0.266(11)	0.431 (9)	0.105 (1)	0.215 (9)	0.007(19)	1.025(13)
454.5	0.250 (9)	0.431 (1)	0.104 (4)	0.193(13)	0.010 (8)	0.989 (6)
652.5	0.260(16)	0.432(12)	0.108 (3)	0.179 (6)	0.001 (2)	0.981(40)
1475.0	0.264 (5)	0.445(18)	0.113 (1)	0.179(10)	0.001 (2)	1.002(33)
2877.0	0.256(16)	0.449(10)	0.108 (5)	0.165 (7)	0.002 (5)	0.979(18)

[a] 0.0687M.

[b] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

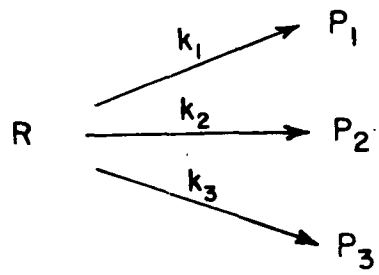
[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[f] 3,4,6-Tri-O-methyl-D-mannopyranose.

Parallel first-order reactions where the reactant (R) goes to two or more products have been described mathematically by Frost and Pearson (21). The constants generated by use of simplified forms of the kinetic equations are valuable for comparison with other systems (1,22).



The integrated form of the rate equation for the pseudo first-order disappearance of reactant is given by Equation (2):

$$\ln X_{r,t} = -k_r t, \qquad (2)$$

where $X_{r,t}$ = mole fraction of reactant at time t

$k_r = \sum_i k_i$ = pseudo first-order specific rate constant for reactant disappearance, sec^{-1}

k_i = pseudo first-order specific rate constant for the formation of product i, sec^{-1}

Appearance of each product is described by Equation (3):

$$\ln (X_{i,\infty} - X_{i,t}) = -k_r t + \ln X_{i,\infty}, \qquad (3)$$

where $X_{i,t}$ = mole fraction of product i at time t

$X_{i,\infty}$ = the relative proportion of product i formed[3]

[3]For parallel first-order reactions, $X_{i,\infty} = X_{i,t}$ at completion (the relative proportion of product i formed). However, as will be shown, the ethanolysis deviated noticeably from parallel first-order kinetics after ca. 60% completion. For this reason, $X_{i,\infty}$ was determined from $X_{i,\infty} = X_{i,t}\sqrt{\sum_i X_{i,t}}$ ($t \leq 10$ min for picric acid-catalyzed ethanolysis).

The value of each individual rate constant, k_i, can be calculated from Equation (4):

$$k_i = k_r X_{i,\infty}. \qquad (4)$$

Thus, a complete description of the parallel first-order kinetics is given by k_r and $X_{i,\infty}$ since any other quantity can be calculated from these quantities and Equations (2)-(4) assuming no other reactions occur.

A parallel first-order plot for the initial disappearance of reactant and appearance of products is shown in Fig. 5. Figure 6 also demonstrates that ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside, and 3,4,6-tri-O-methyl-D-mannopyranose were formed in constant proportions (i.e., parallel reactions) up to ca. 60% reaction of I (10 min). After 10 minutes, the proportions of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-α- and -β-D-mannopyranoside increased at the expense of 3,4,6-tri-O-methyl-D-mannopyranose. The reason for this deviation from parallel first-order kinetics is discussed in a following section.

In addition to the picric acid-catalyzed ethanolysis, ethanolyses catalyzed by (1) 0.005N 2,6-dichlorobenzoic acid (see Appendix III, Table XVI) and (2) 0.005N 2,6-dichlorobenzoic acid in 0.06N lithium p-toluenesulfonate (see Appendix III, Table XVII) were also followed kinetically. The carbohydrate product mole fractions ($X_{i,\infty}$) and rate constants (k_r) are presented in Table III. The values given are based on the early stages of ethanolyses (up to ca. 60% orthoester consumed), because deviations from parallel first-order kinetics were apparent after 60% of the reactant had been consumed.

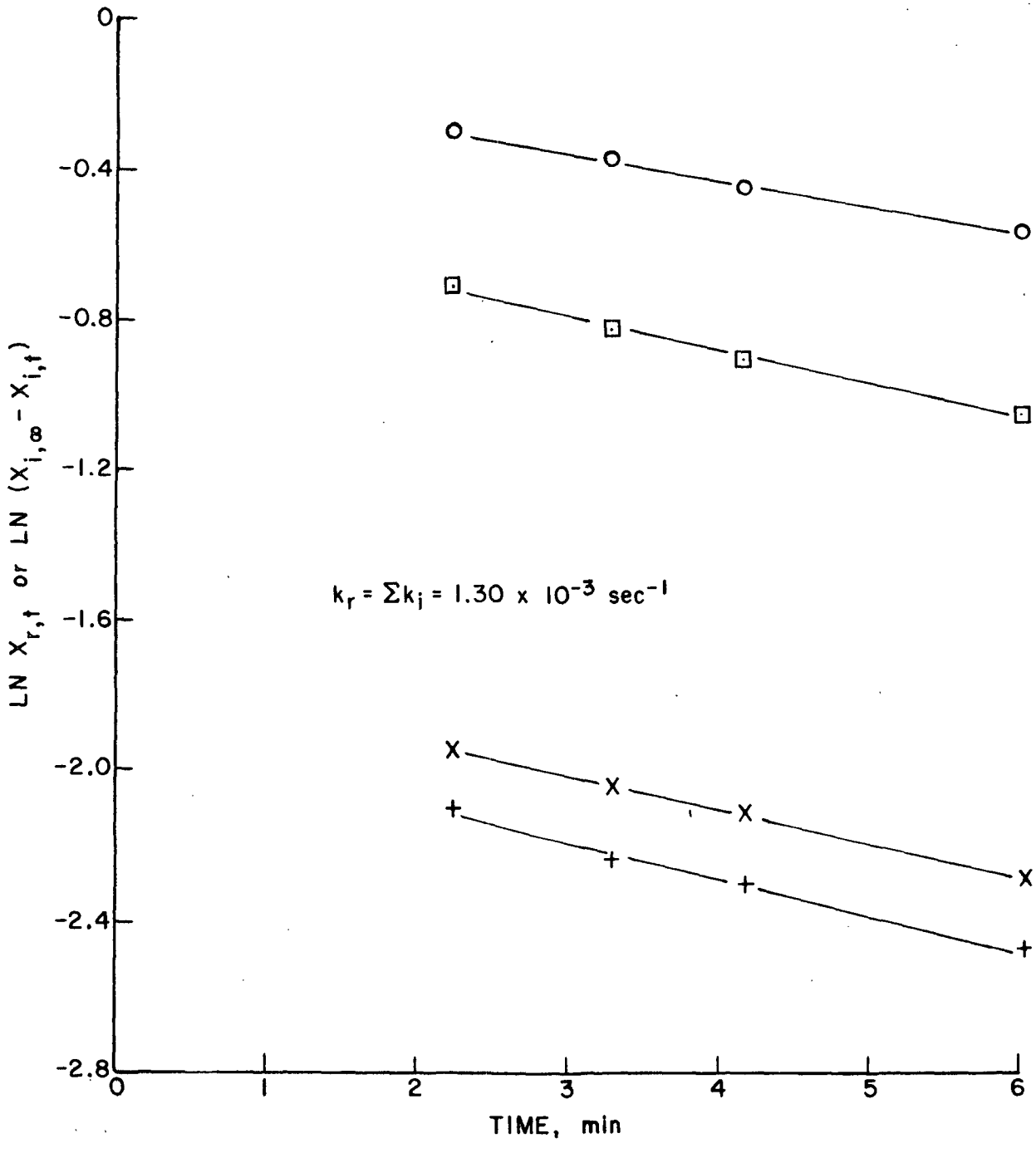


Figure 5. Parallel First-Order Kinetic Plot for 0.00512N Picric Acid-Catalyzed Ethanolysis of 1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, at 25.0°C:

- o 1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose;
- □ Ethyl 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, $X_{1,\infty} = 0.194$;
- x Ethyl 3,4,6-Tri-O-methyl-α-D-mannopyranoside, $X_{2,\infty} = 0.160$;
- \+ 3,4,6-Tri-O-methyl-D-mannopyranose, $X_{3,\infty} = 0.646$

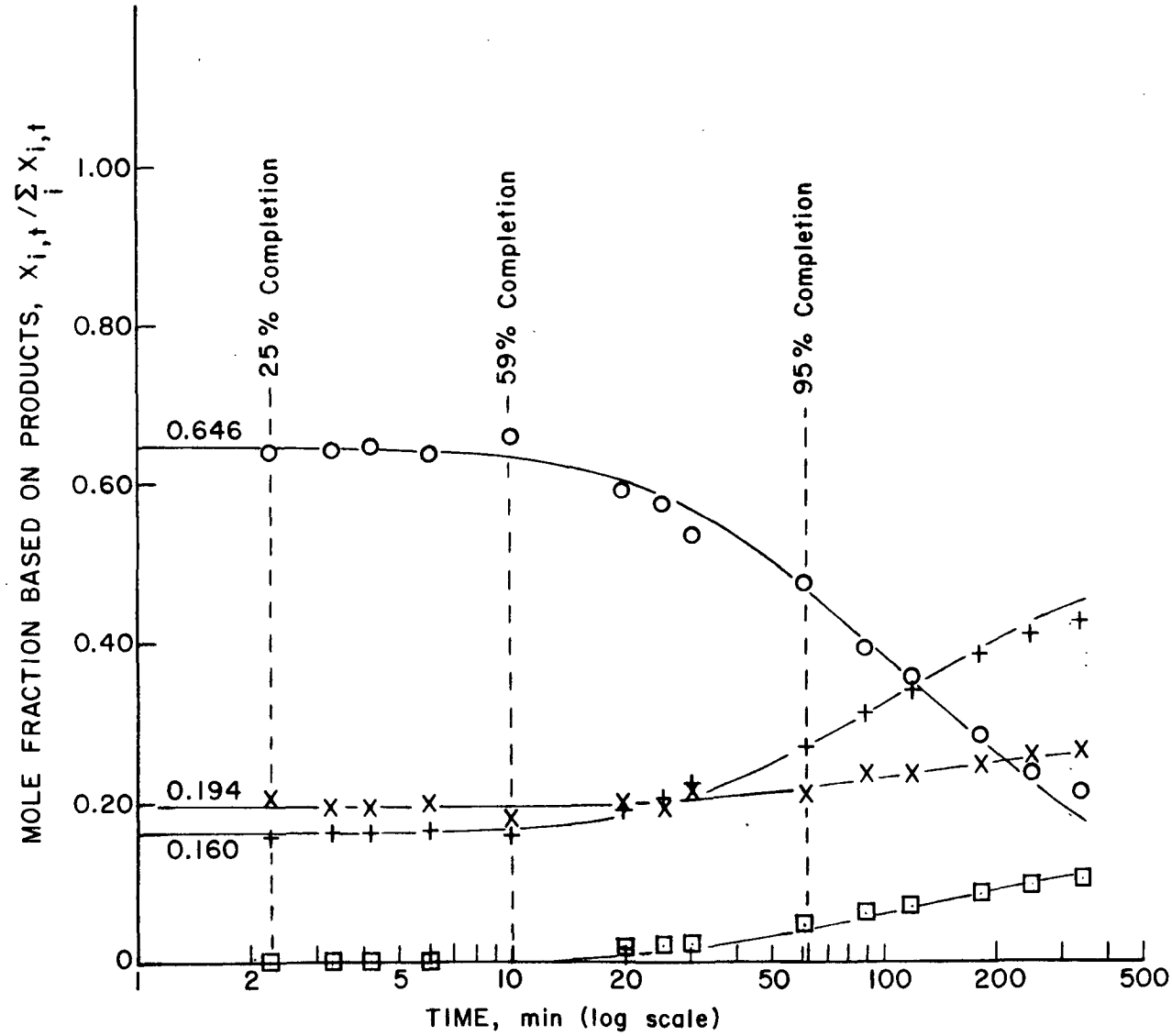


Figure 6. Product Distribution for 0.00512N Picric Acid-Catalyzed Ethanolysis of 1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C:
- o 3,4,6-Tri-O-methyl-D-mannopyranose;
- x Ethyl 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside;
- \+ Ethyl 3,4,6-Tri-O-methyl-α-D-mannopyranoside;
- □ Ethyl 3,4,6-Tri-O-methyl-β-D-mannopyranoside

TABLE III

RATE CONSTANTS AND MOLE FRACTION SUMMARY[a] FOR ETHANOLYSES OF 1,2-O-(1-ETHOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[b] AT 25.0°C

Acid	Salt	Relative Proportion of Carbohydrate Products, mole fraction ($X_{i,\infty}$)					Rate Constant (10^5 k_r, sec^{-1})	Relative Rate
		α Et 2-O-Ac[c]	β Et 2-O-Ac[d]	α Et[e]	β Et[f]	TMM[g]		
0.00512N Picric acid	--	0.194	0.000	0.160	0.000	0.646	130.0	198
0.00528N 2,6-Dichlorobenzoic acid	--	0.178	0.000	0.148	0.000	0.675	0.656	1
0.00535N 2,6-Dichlorobenzoic acid	0.063N lithium p-toluenesulfonate	0.241	0.007	0.165	0.028	0.559	2.84	4.3

[a] The values given are based only on the parallel first-order phase of orthoester disappearance (up to 60% reactant consumed).

[b] 0.068M.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[f] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[g] 3,4,6-Tri-O-methyl-D-mannopyranose.

Effect of the Acid

Although the rate of the picric acid-catalyzed ethanolysis was much greater than that of the 2,6-dichlorobenzoic acid-catalyzed reaction, exo-endo isomerization, formation of glycosides and reducing sugar, and deviations from parallel first-order kinetics occurred in both acid-catalyzed systems. As shown in Table III, there was very little difference in the product distributions of carbohydrates formed in the parallel first-order reactions.

Effect of Lithium p-Toluenesulfonate

In comparing the 0.005N 2,6-dichlorobenzoic acid-catalyzed ethanolysis with the ethanolysis catalyzed by 0.005N 2,6-dichlorobenzoic acid in 0.06N lithium p-toluenesulfonate (see Table III), three noticeable differences were observed: (1) a larger amount of glycosides was formed in the presence of lithium p-toluenesulfonate, (2) the stereoselectivity for α-mannopyranosides was slightly lower in the presence of the salt, and (3) the reaction was faster with lithium p-toluenesulfonate in the system.

Polarimetric Analysis

Ethanolyses of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose were followed by polarimetry, and the results are presented in Appendix I. As shown in the discussion section, polarimetry offered in independent check on the GLC results. In addition, polarimetry offered a technique to determine the anomeric configuration of the 3,4,6-tri-O-methyl-D-mannopyranose formed initially in ethanolyses.

A sample of the reaction solution was quenched at 5.7 minutes by addition of triethylamine to observe the base-catalyzed mutarotation of 3,4,6-tri-O-methyl-D-mannopyranose which had been formed during the acid-catalyzed ethanolysis.

The sample mutarotated upward (+0.06°) to a constant value (see Appendix I, Table XII) proving that the β-anomer must have been formed at least in quantities above that present at the mutarotation equilibrium. Positive proof that only the β-anomer was formed initially was not obtained because of the fast rate of mutarotation of 3,4,6-tri-O-methyl-D-mannopyranose (Appendix I, Table XIII).

Ethyl Acetate and Triethyl Orthoacetate Analyses

Accompanying the formation of 2-hydroxymannopyranosides and reducing sugar was the formation of ethyl acetate and triethyl orthoacetate. Ethyl acetate and triethyl orthoacetate were identified by NMR, and the sum of their mole fractions was quantitatively determined by GLC.

The acid-catalyzed (0.0047N picric acid) ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (0.6M) at 40°C was followed by NMR. Scans ($1.3 \leq \delta \leq 2.3$ ppm) were made at reaction times of ca. 1, 2, 6, 12, and 18 minutes (see Fig. 7). The spectra show decreases in the carbohydrate orthoacetyl methyl singlets at $\delta = 1.63$ (exo-ethoxy) and $\delta = 1.47$ (endo-ethoxy) [exo-endo isomerization occurred before the first scan was made], and increases in the singlets for triethyl orthoacetate ($\delta = 1.42$), ethyl acetate ($\delta = 2.00$), and 2-O-acetyl mannopyranosides ($\delta = 2.08$ ppm) with increasing time.

The methyl singlet of triethyl orthoacetate lies between the endo-ethoxy orthoacetate methyl singlet and the ethoxy methyl triplet. To demonstrate that sufficient resolution could be obtained for triethyl orthoacetate identification, NMR spectra of known samples were made (see Fig. 8).

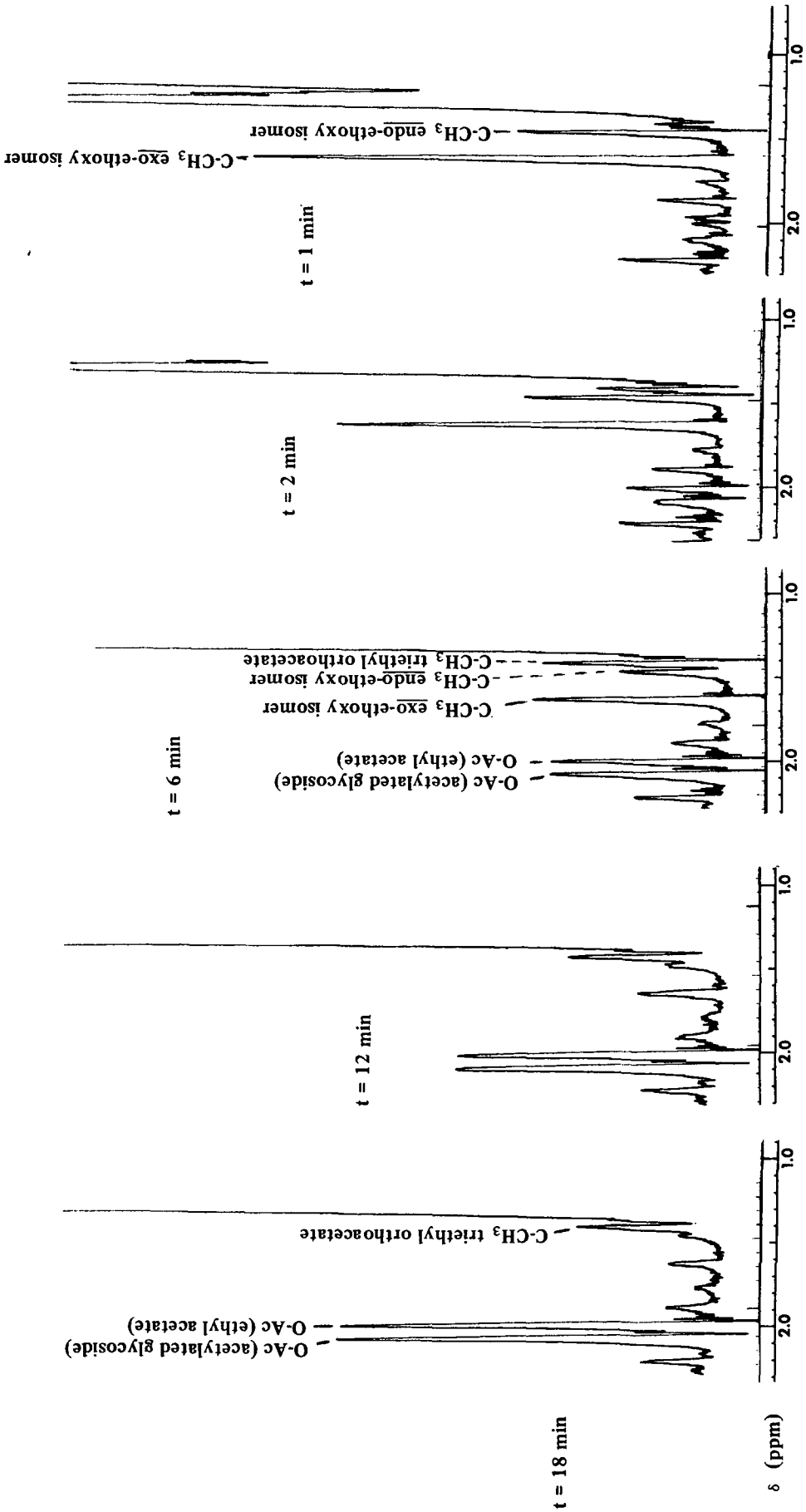


Figure 7. Partial NMR Spectra of an Acid-Catalyzed (0.0047N Picric Acid) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose at 40°C

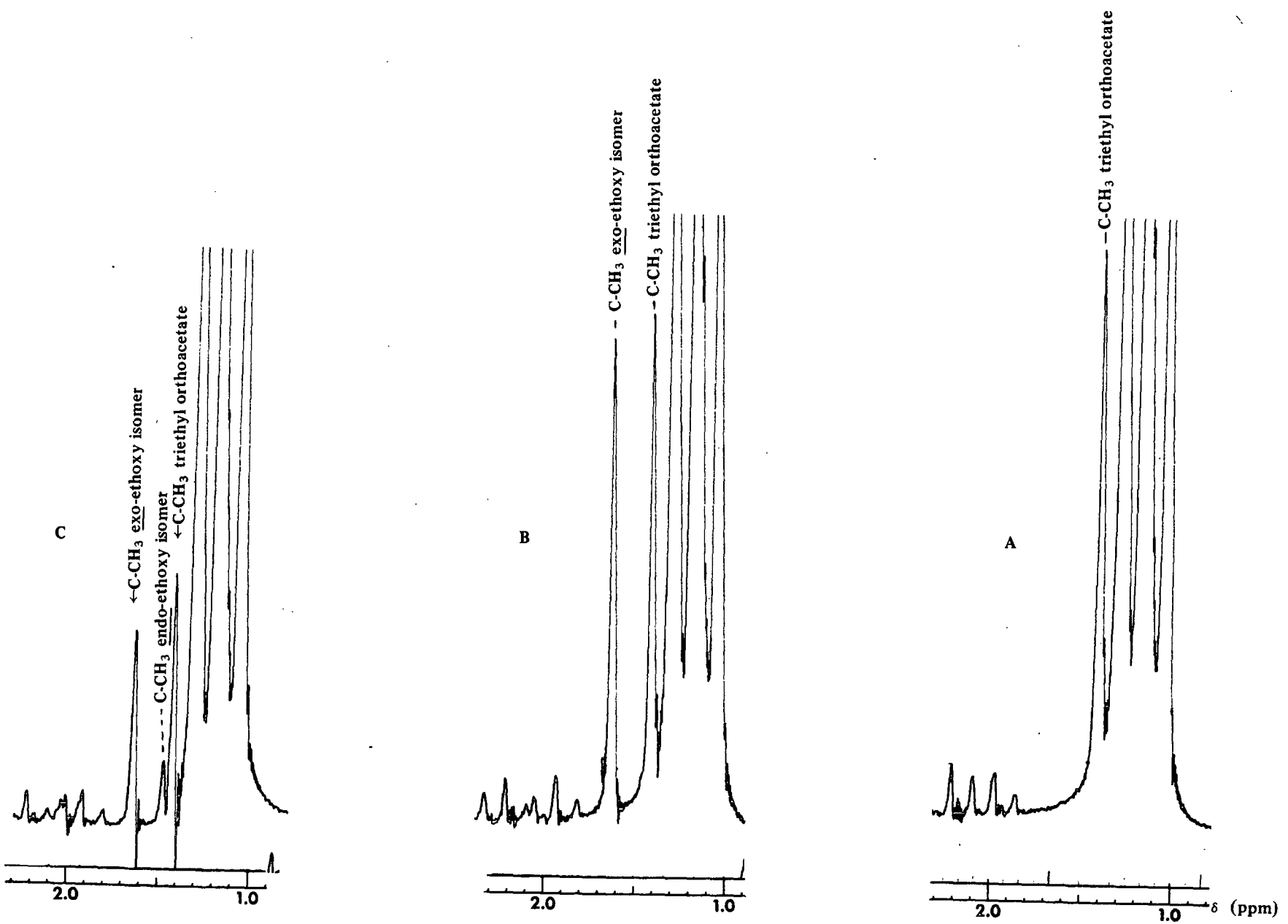


Figure 8. Partial NMR Spectra of Ethanol. A, After Addition of Triethyl Orthoacetate; B, After Addition of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose to A; C, After Addition of Ethanolic Picric Acid to B

Since the usual 0.069M orthoester reaction solution was too dilute for direct NMR analysis, quantitative analysis of ethyl acetate and triethyl orthoacetate was obtained by a GLC method. The GLC procedure involved quantitative hydrolysis of triethyl orthoacetate to ethyl acetate. The mole fraction determined for ethyl acetate, therefore, represented the sum of the mole fractions of ethyl acetate plus triethyl orthoacetate formed in ethanolysis. The data are given in Table IV.

TABLE IV

FORMATION OF ETHYL ACETATE AND TRIETHYL ORTHOACETATE IN A 0.00527N PICRIC ACID-CATALYZED ETHANOLYSIS[a] AT 25.0°C[b]

Time, min	Ethyl Acetate + Triethyl Orthoacetate, mole fraction[c]
7.7	0.453(30)
12.0	0.520(13)
22.8	0.663(27)
142.0	0.760(32)

[a] 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (0.0686M).

[b] GLC data for this kinetic run are given in Appendix III, Table XV; polarimetric data, Appendix I, Table XI.

[c] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

DISAPPEARANCE OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE

In the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, the mole fraction of 3,4,6-tri-O-methyl-D-mannopyranose reached a maximum, then decreased (see Table II). Accompanying the decrease in reducing sugar was a corresponding increase in ethyl mannopyranosides. Two

a priori possibilities for the disappearance of 3,4,6-tri-*O*-methyl-D-mannopyranose were (1) acid-catalyzed Fischer glycosylation, and (2) the formation of 1,2-*O*-(1-ethoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranose or other mannose orthoesters which subsequently undergo ethanolysis to mannopyranosides. The former possibility was eliminated since 3,4,6-tri-*O*-methyl-D-mannopyranose did not yield detectable amounts of glycosides after 42 hours in 25.0°C ethanolic 0.00525*N* picric acid; the results in Table II indicate that the mole fraction of 3,4,6-tri-*O*-methyl-D-mannopyranose decreased from 0.50 to 0.29 in 2.5 hours.

The hypothesis that 3,4,6-tri-*O*-methyl-D-mannopyranose reacts to form mannopyranose orthoesters by transorthoesterification with triethyl orthoacetate and that these intermediates subsequently undergo ethanolysis to form mannopyranosides was confirmed using 3,4,6-tri-*O*-methyl-D-mannopyranose (a mutarotated equilibrium mixture) and triethyl orthoacetate in ethanolic 0.0053*N* picric acid at 25.0°C. Although the ethanolysis of 1,2-*O*-(1-ethoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranose formed the β-anomer of 3,4,6-tri-*O*-methyl-D-mannopyranose, the relatively fast rate of mutarotation (compared to glycoside formation from the reducing sugar) justified the use of an anomeric mixture of the reducing sugar in this study.

Carbohydrate Analysis

Data in Table V illustrate carbohydrate products and reactant analyses as a function of time for the 0.00526*N* picric acid-catalyzed ethanolysis of 3,4,6-tri-*O*-methyl-D-mannopyranose in the presence of triethyl orthoacetate at 25.0°C. The initial products of the reaction were ethyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-*O*-methyl-β-D-mannopyranoside, and mannose orthoester intermediates. After an induction period (10-15 min), ethyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-mannopyranoside was detected. Data for an additional ethanlysis are given in Appendix V, Table XX.

TABLE V

ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE[a] IN THE PRESENCE OF TRIETHYL ORTHOACETATE[b] IN 0.00526N PICRIC ACID AT 25°C

Time, min	Mole Fraction[c]					
	Products			Intermediate[d]	Reactant[d]	Total
	α Et 2-O-Ac[e]	α Et[f]	β Et[g]	Orthoesters[h]	TMM[i]	Measured
2.3	0.000 (0)	0.029(10)	0.011(14)	0.026(17)	0.977(14)	1.043(28)
5.4	0.000 (0)	0.062(10)	0.029 (3)	0.058(17)	0.888(11)	1.037(22)
9.4	0.000 (0)	0.102(13)	0.044 (5)	0.095 (3)	0.756 (5)	0.998(22)
15.7	0.010 (2)	0.155(12)	0.068 (4)	0.115 (9)	0.677 (7)	1.026(20)
25.0	0.029 (1)	0.230 (3)	0.095 (2)	0.120 (1)	0.563 (7)	1.037 (7)
36.7	0.051 (5)	0.301 (6)	0.120 (3)	0.113 (6)	0.480(14)	1.066(33)
54.5	0.069 (4)	0.358 (7)	0.140 (5)	0.086(11)	0.339 (4)	0.992(27)
81.6	0.096 (6)	0.436(17)	0.175 (2)	0.052 (7)	0.274 (5)	1.032(11)
112.9	0.106 (6)	0.522(15)	0.194 (4)	0.022(11)	0.186 (4)	1.029(15)
181.3	0.141 (4)	0.573(12)	0.217 (6)	0.000 (0)	0.095 (3)	1.025(10)
366.8	0.150 (7)	0.640(27)	0.242(15)	0.000 (0)	0.006 (6)	1.038(46)

[a] 0.0602M.

[b] 0.1123M.

[c] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[d] Intermediate and reactant values are minimum and maximum values, respectively.

[e] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[f] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[g] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[h] 1,2-O-(1-Ethoxyethylidene), 2-O-(1,1-diethoxyethyl)-, and 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-D-mannopyranose are potential intermediates.

[i] 3,4,6-Tri-O-methyl-D-mannopyranose.

Intermediate mannopyranose orthoesters were detected and estimated by the measurement of mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses after subjecting the sample to a hydrolysis procedure. Since acid hydrolyses of some potential mannose orthoesters [2-O-(1,1-diethoxyethyl)- and 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-D-mannopyranoses] would be expected to yield 3,4,6-tri-O-methyl-D-mannopyranose as well as mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses (1,23), the measurements of mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses must be interpreted as minimum estimates of the mannose orthoester intermediates. Also, for this reason, 3,4,6-tri-O-methyl-D-mannopyranose analyses represent maximum values for the amounts detected in the system.

Kinetics

1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose is the only intermediate which can account for ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside formation in the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate. However, if it had been the only intermediate forming mannopyranosides, the mannopyranoside product distribution (Table V) would have been very similar to that found for the parallel first-order appearance of glycosides from the ethanolysis of the mannose 1,2-(ethyl orthoacetate) (Table II). The mannopyranose product distributions for the two systems were different. Thus, a portion of the glycosides formed in the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate must have been formed by other routes.

Based on the product distributions for ethanolyses of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose and of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate, the scheme illustrated in Fig. 9 is suggested for the latter reaction.

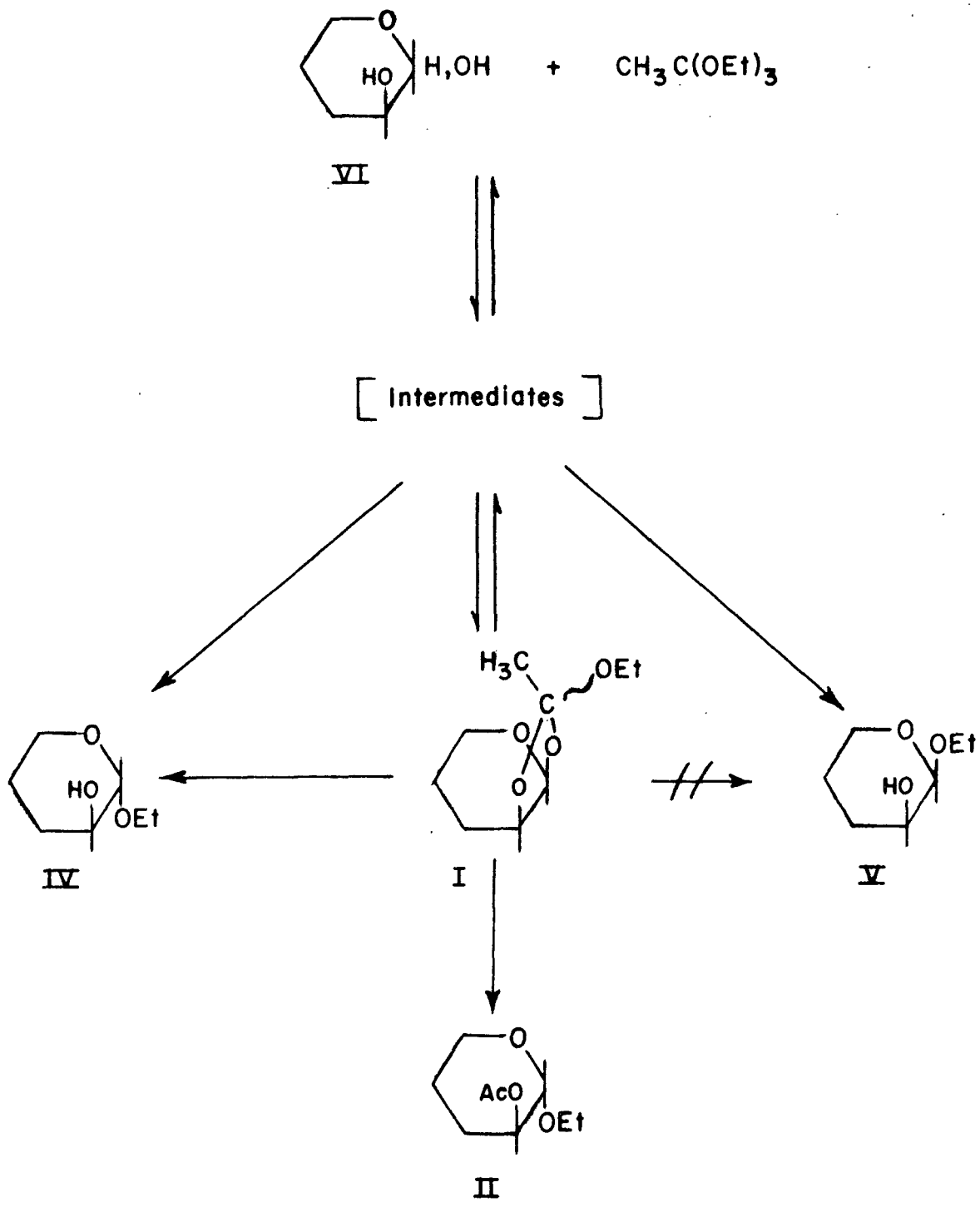


Figure 9. Suggested Reaction Scheme for the Acid-Catalyzed Ethanolysis of 3,4,6-Tri-O-methyl-D-mannopyranose in the Presence of Triethyl Orthoacetate (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

The three products (I, IV, and V) formed "directly" from the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate were formed in constant proportions (i.e., in parallel reactions). Several calculations are necessary, however, to demonstrate the parallel nature of the reactions because 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose was not a stable product.

Glycose 1,2-(alkyl orthoacetates) are considerably less reactive in aqueous acid solutions than are acyclic orthoacetates (19). The acid-catalyzed ethanolysis of the acyclic orthoester, 1-O-(1,1-diethoxyethyl)-2,3,4,6-tetra-O-methyl-α-D-glucopyranose (1,23), is at least 100 times faster than that of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose. Thus, it is reasonable to assume that the acyclic orthoester intermediates are much more reactive than the mannose 1,2-(ethyl orthoacetate). Therefore, the mannose orthoester intermediates detected at time t should be approximately equal to the 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose present in the system at time t.

The parallel first-order phase of the 0.005N picric acid-catalyzed ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose indicated that 0.194 mole of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside were formed for every mole of reactant consumed. By analogy with the glucose system (1), all the ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside detected in the ethanolysis of the reducing sugar must have been formed from 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose. Thus, the mole fraction of the mannose 1,2-(ethyl orthoacetate) (I) that had reacted at time t is given by Equation (5):

$$\text{mole fraction I reacted (t)} = \text{mole fraction II detected (t)}/0.194, \quad (5)$$

where I = 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose

II = ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside

The total mole fraction of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose that had been formed at time t is given by Equation (6):

$$\begin{aligned} X_{4,t} &= \text{mole fraction I reacted (t)} + \text{mole fraction I formed but not reacted} \\ &= \text{mole fraction II detected (t)}/0.194 + \text{mole fraction of mannose orthoester intermediates detected (t)}, \end{aligned} \tag{6}$$

where $X_{4,t}$ = mole fraction of I that had been formed at time t.

The ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside detected in the reaction represents that formed "directly" from the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose[4] plus that formed from 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (see Fig. 9). The parallel first-order phase of the picric acid-catalyzed ethanolysis of the mannose 1,2-(ethyl orthoacetate) indicated that 0.160 mole of ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside were formed for every mole of reactant consumed. The mole fraction of ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside formed "directly" from the ethanolysis of the reducing sugar is given by Equation (7):

$$\begin{aligned} X_{5,t} &= \text{mole fraction IV detected (t)} - \text{mole fraction formed from I (t)} \\ &= \text{mole fraction IV detected (t)} - 0.160\ \{[\text{mole fraction II detected (t)}]/0.194\}, \end{aligned} \tag{7}$$

where $X_{5,t}$ = mole fraction of IV formed "directly"

IV = ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside

[4] The phrase "formed 'directly' from the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose" refers to products formed from intermediates other than the mannose 1,2-(ethyl orthoacetate).

Equations (5)-(7) are based on the assumption that the presence of the high and changing concentration of triethyl orthoacetate does not cause a significant change in the product distribution from the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose.

The parallel first-order phase of the picric acid-catalyzed ethanolysis of the mannose 1,2-(ethyl orthoacetate) did not yield ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside. Thus, the mole fraction of ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (V) formed "directly" from the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate ($X_{6,t}$) was equal to the mole fraction detected.

To demonstrate that the products (I, IV, and V) were formed in parallel reactions, one must show that the relative proportion of each product was time independent (21). That is, the mole fraction of product j at time t,

$$X_{j,t}/(X_{4,t} + X_{5,t} + X_{6,t})$$

was independent of time. Figure 10 illustrates that the products (I, IV, and V) formed in the acid-catalyzed ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate were formed in parallel reactions.

The formation of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose was reversible and thus complicated the kinetic treatment. Nevertheless, it can be demonstrated (see Appendix VI) that the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate was first-order in both the reducing sugar and orthoester. The pseudo second-order rate constants found were the following:

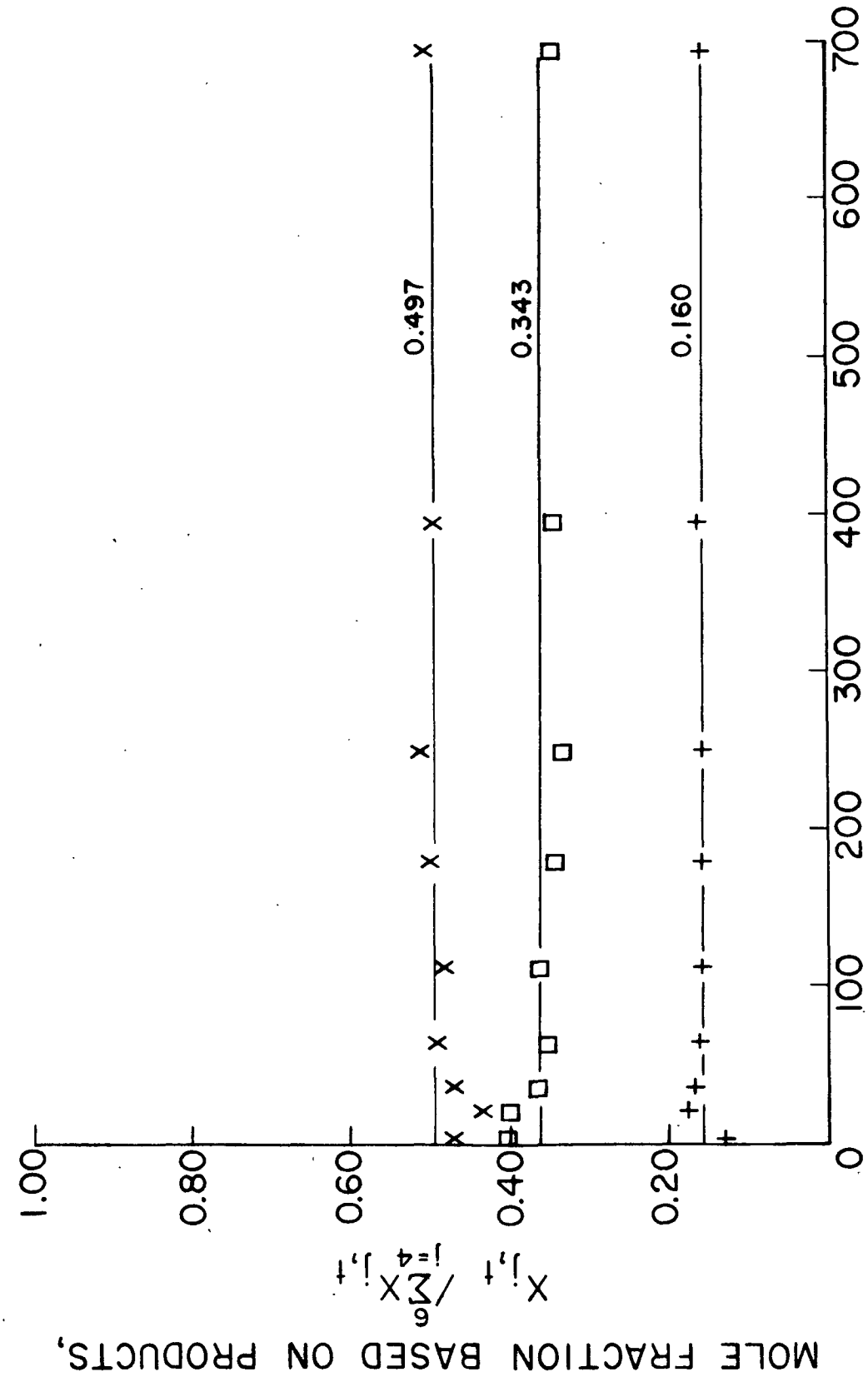


Figure 10. Parallel Product Formation in a Picric Acid (0.00531N)-Catalyzed Ethanolysis of 3,4,6-Tri-O-methyl-D-mannopyranose (0.091OM) in the Presence of Triethyl Orthoacetate (0.1121M) at 25.0°C:

x 1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose;

□ Ethyl 3,4,6-Tri-O-methyl-α-D-mannopyranoside;

\+ Ethyl 3,4,6-Tri-O-methyl-β-D-mannopyranoside

$\underline{k}_4 = 2.34 \times 10^{-3}$ (liters/mole-sec),

$\underline{k}_5 = 1.61 \times 10^{-3}$ (liters/mole-sec),

$\underline{k}_6 = 0.752 \times 10^{-3}$ (liters/mole-sec),

$\underline{\underline{k}}_{rs} = \sum_{j=4}^{6} \underline{k}_j = 4.70 \times 10^{-3}$ (liters/mole-sec),

where $\underline{k}_j$ = second-order specific rate constants for the formation of product $\underline{j}$ ($\underline{j}$ = 4,5,6)

4 = 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-manno-pyranose

5 = ethyl 3,4,5-tri-O-methyl-α-D-mannopyranoside

6 = ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside

$\underline{\underline{k}}_{rs}$ = second-order specific rate constant for the disappearance of 3,4,6-tri-O-methyl-D-mannopyranose and triethyl orthoacetate

ACID-CATALYZED REACTIONS WITH ETHANOL IN VARIOUS SOLVENTS

The effects of the solvent and the initial alcohol concentration on the product distributions of acid-catalyzed reactions of 1,2-O-[1-(exo-ethoxy)-ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose with ethanol were studied. Each reaction was followed by NMR, and was quenched when 90-95% of the mannose 1,2-(ethyl orthoacetate) was consumed. Results of GLC analyses of the samples are given in Table VI. These product distributions were affected to some degree by secondary reactions of 3,4,6-tri-O-methyl-D-mannopyranose with triethyl orthoacetate and ethanol. Nevertheless, NMR spectra of the initial portions of the seven reactions studied (when the effects of the secondary reasons were not significant) exhibited the same general trends in product distributions indicated in Table VI. Figure 7 illustrates a series of spectra obtained for one of the reactions studied.

The data in Table VI indicate that, at a constant orthoester concentration, decreasing the initial ethanol concentration (1) decreased

TABLE VI

EFFECT OF SOLVENT AND ETHANOL CONCENTRATION ON THE PRODUCT DISTRIBUTION OF THE REACTIONS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE (0.6M) WITH ETHANOL AT 40°C IN 0.00467N PICRIC ACID

Solvent	Initial Ethanol: Orthoester Molar Ratio	Mole Fraction Orthoester Left when Quenched (time in min)	Product Distribution, mole fraction[a,b]				
			α Et 2-O-Ac[c]	β Et 2-O-Ac[d]	α Et[e]	β Et[f]	TMM[g]
Dichloromethane	2:1	0.067(140)	0.660(14)	0.040 (1)	0.198 (7)	0.089 (3)	0.013 (3)
Dichloromethane	5:1	0.057(130)	0.629(12)	0.028 (2)	0.236(12)	0.069 (3)	0.038 (2)
Dichloromethane	10:1	0.083 (65)	0.534 (5)	0.014 (3)	0.307 (5)	0.076 (2)	0.069 (5)
Dichloromethane	20:1	0.047 (25)	0.457 (8)	trace	0.352(20)	0.064 (9)	0.128 (7)
Ethanol	25:1	0.094 (20)	0.447 (7)	0.000	0.336 (3)	0.058 (3)	0.161(11)
Nitromethane	2:1	0.000 (43)[h]	0.558 (2)	0.011 (5)	0.288(10)	0.143 (8)	0.000
Nitromethane	20:1	0.078 (16)	0.441 (2)	0.000	0.379 (7)	0.065 (5)	0.114 (6)

[a] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[b] Normalized data.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[f] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[g] 3,4,6-Tri-O-methyl-D-mannopyranose.

[h] The reaction was not quenched when desired.

3,4,6-tri-O-methyl-D-mannopyranose formation relative to glycoside formation, (2) decreased 2-hydroxyglycoside formation relative to 2-O-acetyl-glycoside formation, and (3) decreased the stereoselectivity for formation of the α-glycosides. The data also indicate that the ratio of 2-O-acetyl-glycoside to 2-hydroxyglycoside formed decreased (at constant alcohol concentrations) as the solvent polarity increased. Although the effect of temperature was not extensively studied, increasing the temperature increased the formation of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside significantly (compare the product distributions for ethanolysis at 25.0°C, Table II, with that at 40°C, Table VI).

ACID-CATALYZED REACTIONS IN AQUEOUS ETHANOL

Prior to GLC analysis of the carbohydrate products and reactant, ethanolysis samples were chemically modified to change the unreacted orthoester and carbohydrate products to derivatives which were suitable for GLC analysis. One phase of the chemical modification involved hydrolysis of unreacted 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose. To demonstrate the usefulness of this procedure, reactions of the mannopyranose orthoester in aqueous ethanol were studied. Product analyses are given in Table VII.

The dominant products of the acid-catalyzed hydrolysis of the mannose orthoester were mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses (97 mole%). In anhydrous ethanol, no mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses were formed. Thus, the unreacted orthoester in an ethanolysis could be estimated from the mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses detected after subjecting a sample of the reaction to an appropriate hydrolysis procedure.

3,4,6-Tri-O-methyl-D-mannopyranose was a major product in anhydrous ethanolysis, and a minor product in hydrolysis. Thus, in GLC analysis of

TABLE VII

ACID-CATALYZED REACTIONS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE IN ETHANOL-WATER[a]

Water, mole %	Time, min	Mole Fraction[b] Products					
		α Et 2-O-Ac[c]	α Et[d]	β Et[e]	TMM[f]	TMM Monoacetate[g]	Total Measured
0.0	653	0.260(16)	0.432(12)	0.180 (3)	0.179 (6)	0.001 (2)	0.981(40)
5.2	110	0.000	0.000	0.000	0.064(17)	0.942(16)	1.006(10)
5.2	410	trace	trace	0.000	0.066(11)	0.893 (7)	0.959 (7)
49.8	105	0.000	0.000	0.000	0.026(11)	0.989(22)	1.015(33)
49.8	410	0.000	0.000	0.000	0.043 (3)	0.954(19)	0.997(16)
100.0	422	0.000	0.000	0.000	0.029(16)	0.943 (5)	0.972(21)

[a] 0.005N Picric acid; 0.068M 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose.

[b] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[f] 3,4,6-Tri-O-methyl-D-mannopyranose.

[g] 2-O-Acetyl- and 1-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose.

ethanolysis samples, the amount of 3,4,6-tri-O-methyl-D-mannopyranose detected had to be corrected for that obtained by hydrolysis of unreacted mannose 1,2-(ethyl orthoacetate) to calculate the mole fraction of 3,4,6-tri-O-methyl-D-mannopyranose formed in ethanolysis (see Appendix IV).

The results in Table VII clearly demonstrate the drastic effect of water on ethanolysis, and the need for anhydrous conditions. Small amounts of water would also affect the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate since triethyl orthoacetate is very susceptible to acid hydrolysis.

ACID-CATALYZED HYDROLYSES OF ETHYL 2-O-(1,1-DIETHOXYETHYL)-3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSIDE IN VARIOUS SOLVENTS

Ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside, contaminated with triethyl orthoacetate (see Fig. 11), was subjected to acid-catalyzed hydrolyses in various solvents. The products of the reactions were ethyl 2-O-acetyl- and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside. The results, given in Table VIII, indicate that increasing the solvent polarity increased the formation of ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside relative to its acetylated analog. As will be discussed (see Discussion), the results of this study give supporting evidence for one of the mechanisms proposed for glycoside formation in reactions of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose.

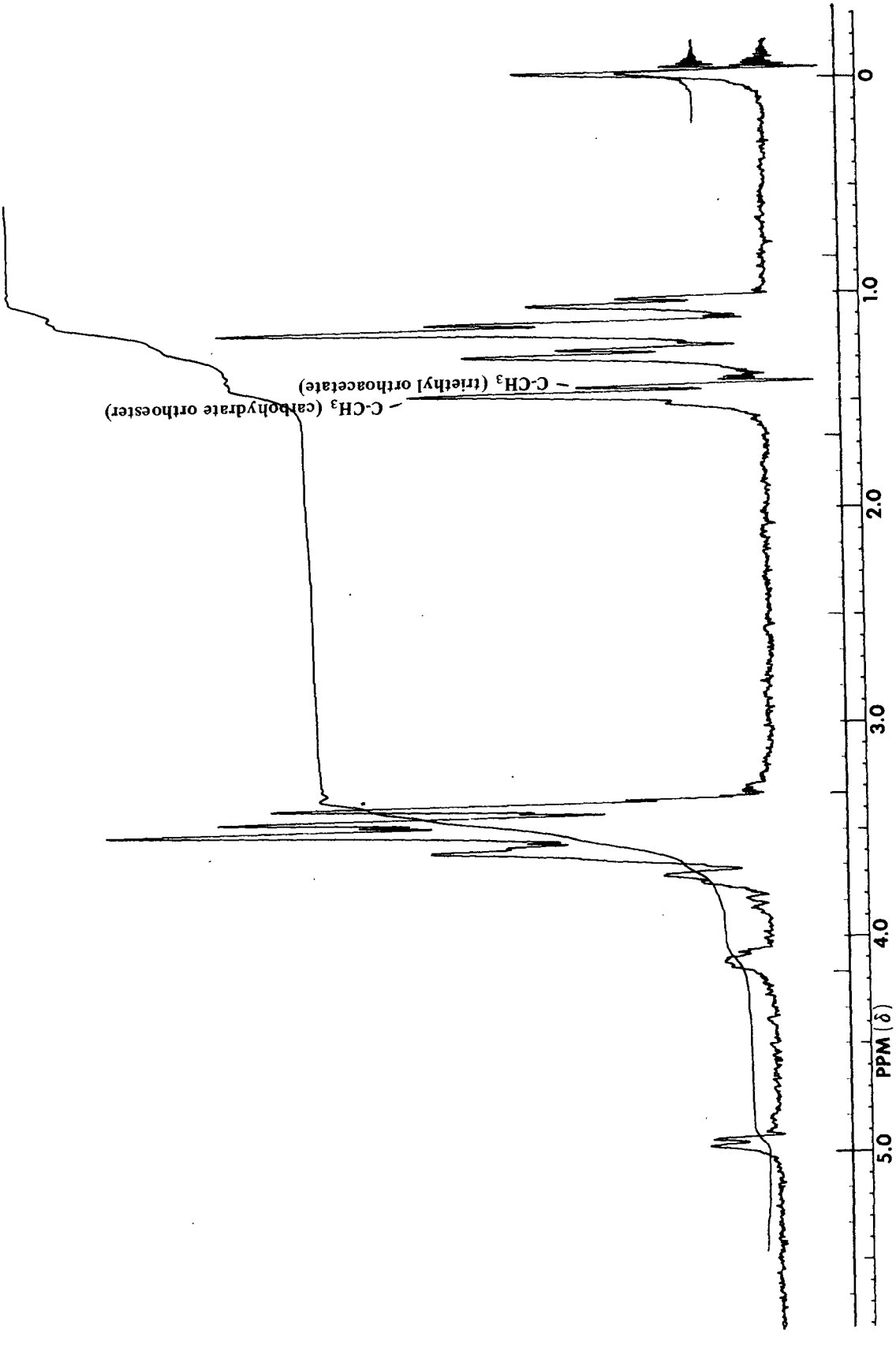


Figure 11. NMR Spectrum ($CDCl_3$) of Ethyl 2-O-(1,1-Diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside Contaminated with Triethyl Orthoacetate

TABLE VIII

ACID-CATALYZED HYDROLYSES OF ETHYL 2-O-[1,1-DIETHOXYETHYL]-3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSIDE IN VARIOUS SOLVENTS

Solvent	Reaction Temp., °C	Dielectric Constant of Solvent	Acid, N	Water, M	Initial Orthoester Concn.[a], M	Product Distribution,[b] mole fraction	
						α Et 2-O-Ac[c]	α Et[d]
Chloroform-d	40	4.8 (at 20°C)	HCl[e]	e	e	0.712	0.288
Ethyl ether	25.0	4.3 (at 20°C)	Picric, 0.0051	0.90	0.064	0.545	0.455
Ethanol	25.0	24.3 (at 25°C)	Picric, 0.0050	0.91	0.061	0.500	0.500
Nitromethane	25.0	35.9 (at 30°C)	Picric, 0.0049	0.90	0.069	0.281	0.719
Water	25.0	78.5 (at 25°C)	Picric, 0.0049	55.3	0.059	0.230	0.770

[a] These values are corrected for the triethyl orthoacetate impurity.

[b] Normalized data.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[e] D_2O and a trace of HCl gas (amounts not measured) were added to an NMR tube containing the orthoester in $CDCl_3$. The D_2O was not very soluble in the chloroform-d solution.

DISCUSSION

MATHEMATICAL MODEL FOR ETHANOLYSIS

A kinetic model of the 0.005N picric acid-catalyzed ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, including the secondary ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate, was developed from analyses (GLC) of various segments of the reaction.

Experimentally, exo-endo isomerization of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose was found to be fast relative to mannose orthoester disappearance (9:1)[5]. Therefore, in the kinetic model, it was assumed that mannopyranose orthoester existed as an equilibrium mixture of the two isomers which behaved kinetically as a single compound.

In the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I), the disappearance of reactant resulted in the parallel first-order appearance of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside (II), ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (IV) (and ethyl acetate), and 3,4,6-tri-O-methyl-D-mannopyranose (VI) (and triethyl orthoacetate) initially (see Fig. 12). The ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose (VI) in the presence of triethyl orthoacetate formed 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I), ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (IV), ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (V), and ethyl acetate in parallel reactions (see Fig. 12). The latter reaction was first-order in both the reducing sugar and triethyl orthoacetate. In the former reaction, the β-isomer of 3,4,6-tri-O-methyl-D-mannopyranose was initially formed. However,

---

[5] $[(k_{\text{exo}\rightarrow\text{endo}})\ (0.73) + (k_{\text{endo}\rightarrow\text{exo}})\ (0.27)]/k_r = 9$ (see Table III and Appendix II).

the relatively fast rate of mutarotation (compared to glycoside formation from the reducing sugar) justified treating the anomeric mixture of 3,4,6-tri-O-methyl-D-mannopyranose as one compound (as indicated in Fig. 12).

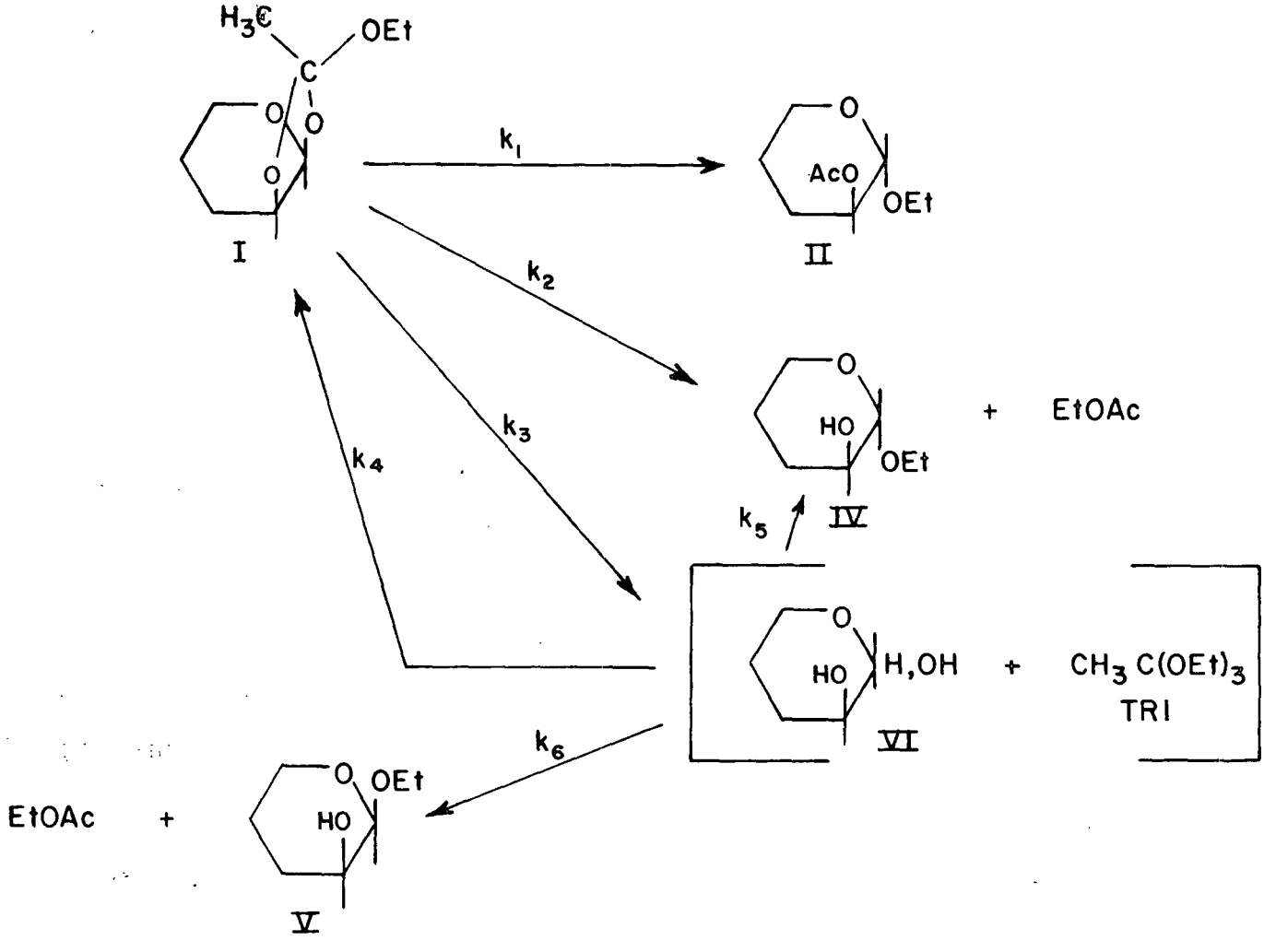


Figure 12. Schematic Diagram of the Mathematical Model for Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

The following differential equations are based on the schematic diagram in Fig. 12:

$$\frac{d[I]}{dt} = -(k_1 + k_2 + k_3)[I] + k_4[VI][TRI], \tag{8}$$

$$\frac{d[II]}{dt} = k_1[I], \tag{9}$$

$$\frac{d[IV]}{dt} = k_2[I] + k_5[VI][TRI], \tag{10}$$

$$\frac{d[V]}{dt} = k_6[VI][TRI], \tag{11}$$

$$\frac{d[VI]}{dt} = -(k_4 + k_5 + k_6)[VI][TRI] + k_3[I], \tag{12}$$

$$\frac{d[EtOAc]}{dt} = \frac{d[IV]}{dt} + \frac{d[V]}{dt}, \tag{13}$$

$$\frac{d[TRI]}{dt} = \frac{d[VI]}{dt}, \tag{14}$$

where TRI = triethyl orthoacetate. The following pseudo first-order and second-order rate constants, which are experimentally determined (see Results and Appendix VI), were used for the kinetic simulation:

$k_1 = 8.40 \times 10^{-4}$ sec^{-1},

$k_2 = 2.52 \times 10^{-4}$ sec^{-1},

$k_3 = 2.08 \times 10^{-4}$ sec^{-1},

$k_4 = 2.34 \times 10^{-3}$ liters/mole-sec,

$k_5 = 1.61 \times 10^{-3}$ liters/mole-sec,

$k_6 = 0.752 \times 10^{-3}$ liters/mole-sec.

The concentrations for I, II, IV, V, and VI were then calculated as a function of time for this model. The computer program used is outlined in Appendix VII.

Comparisons between simulations based on the kinetic model and experimental data are given in Fig. 13-16. In each figure the symbols represent experimentally determined values; the solid lines represent the corresponding simulated values. Equally good fits were obtained for duplicate runs.

As Fig. 13 illustrates, the kinetic model accurately describes the picric acid-catalyzed ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4-6-tri-O-methyl-β-D-mannopyranose up to 350 minutes. At longer times, the simulated values for

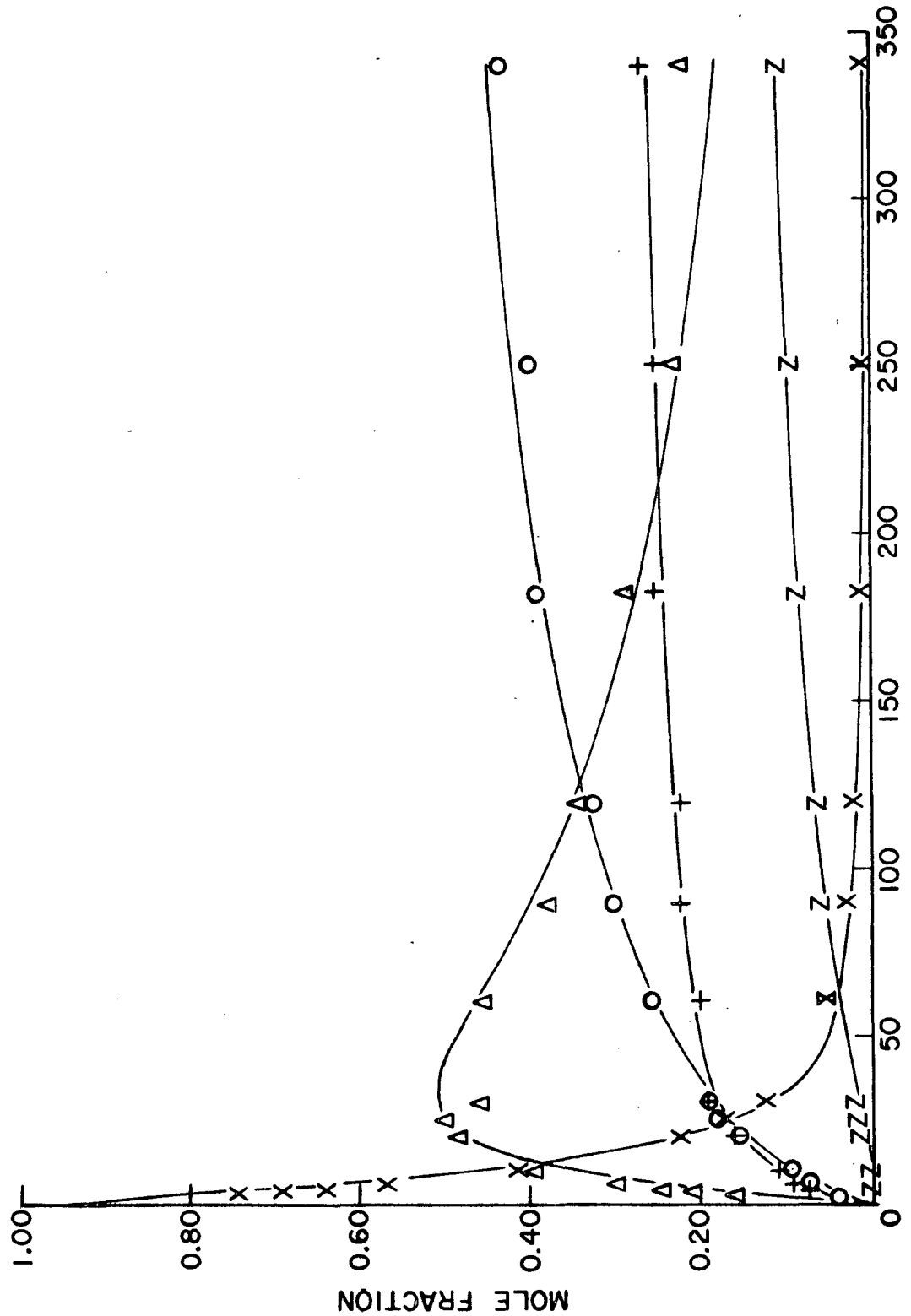


Figure 13. Carbohydrate Analyses. Picric Acid-Catalyzed (0.005N) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C:

x 1,2-O-(1-Ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranoside;
+ Ethyl 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-mannopyranose;
o Ethyl 3,4,6-Tri-O-methyl-α-D-mannopyranoside;
z Ethyl 3,4,6-Tri-O-methyl-β-D-mannopyranoside;
Δ 3,4,6-Tri-O-methyl-D-mannopyranose;
— Simulation

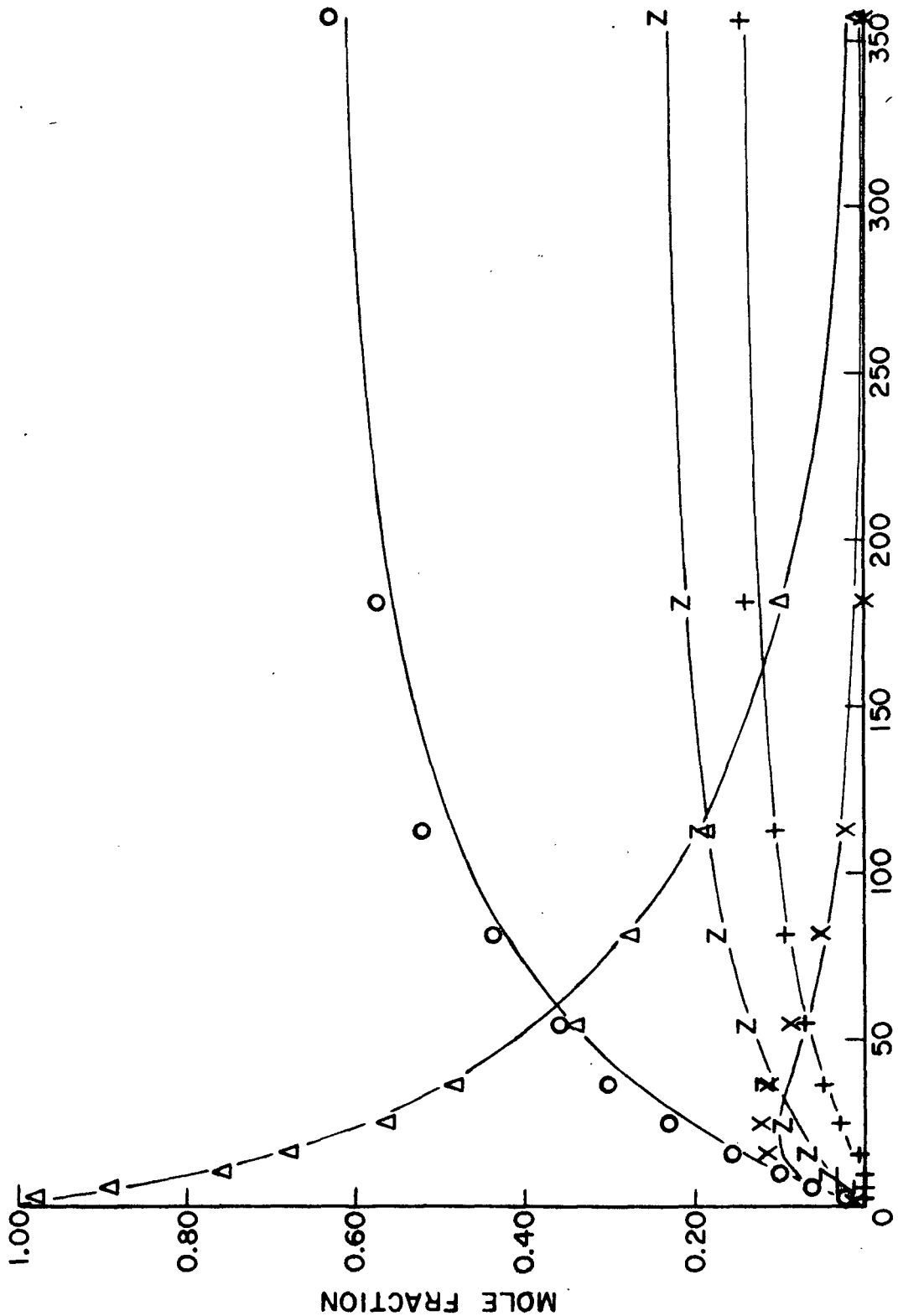


Figure 14. Carbohydrate Analyses. Picric Acid-Catalyzed (0.005N) Ethanolysis of 3,4,6-Tri-O-methyl-D-mannopyranose in the Presence of Triethyl Orthoacetate at 25.0°C:

x 1,2-O-(1-Ethoxyethylidene)-2-O-(1,1-diethoxyethyl)- and 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-D-mannopyranose;
+ Ethyl 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside;
o Ethyl 3,4,6-Tri-O-methyl-α-D-mannopyranoside;
z Ethyl 3,4,6-Tri-O-methyl-β-D-mannopyranoside;
Δ 3,4,6-Tri-O-methyl-D-mannopyranose;
— Simulation

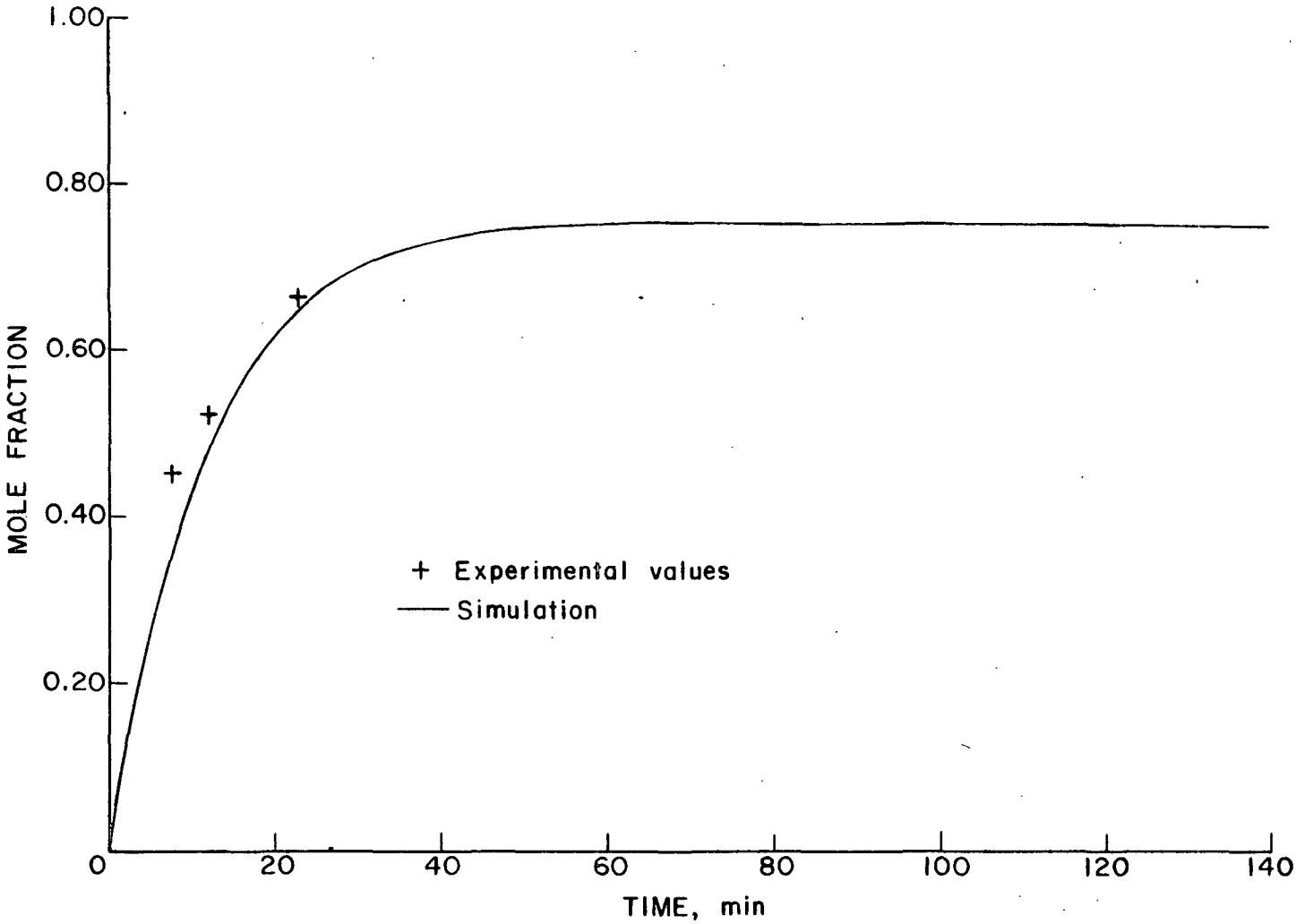


Figure 15. Ethyl Acetate Plus Triethyl Orthoacetate Formation in Picric Acid-Catalyzed (0.005N) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C

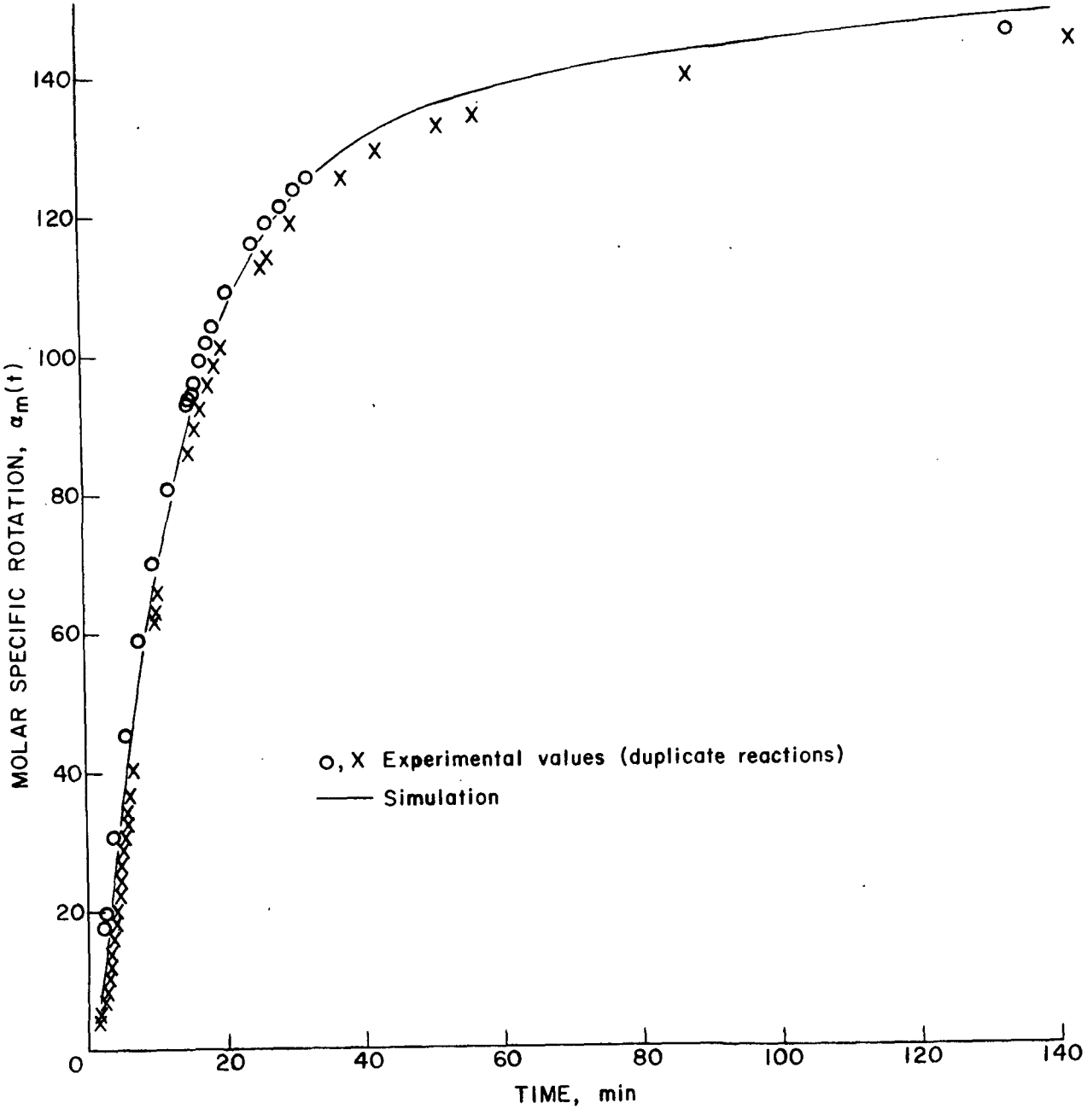


Figure 16. Polarimetric Data. Picric Acid-Catalyzed (0.005N) Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose at 25.0°C (Duplicate Runs)

the mole fraction of 3,4,6-tri-O-methyl-D-mannopyranose decrease more rapidly than the experimental values. At least part of the differences can be accounted for by hydrolysis of triethyl orthoacetate, since the kinetic model assumes that this reaction did not occur. Minute amounts of water could have been introduced during sampling (15 samples were taken during the first 500 minutes of reaction).

Figure 14 illustrates that the kinetic model accurately gave the product distribution when 3,4,6-tri-O-methyl-D-mannopyranose and triethyl orthoacetate were the initial reactants. This result gives further proof that the kinetic model in Fig. 12 represents the overall reaction accounting for product formation in the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose.

Figure 15 illustrates the comparison of the kinetic model with the experimentally determined sum of ethyl acetate plus triethyl orthoacetate as a function of time. The experimental data and the kinetic model agree within the accuracy of the experimental data.

The kinetic model, which is based on carbohydrate analyses (GLC), and experimentally determined specific optical rotations of the carbohydrates (see Appendix I, Table XIV) were used to simulate the molar specific rotation of the ethanolysis of the mannose 1,2-(ethyl orthoacetate) as a function of time. The specific optical rotations used for 3,4,6-tri-O-methyl-D-mannopyranose and 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose were those for the anomeric equilibrium mixture and the exo-endo equilibrium mixture, respectively. In Fig. 16 the simulated polarimetric data are compared with the actual polarimetric data for two duplicate ethanolyses. The agreement of the observed data with the simulated data indicates that the

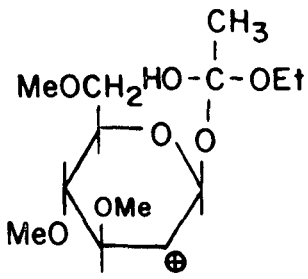
polarimetric results were consistent with the kinetic model and, therefore, with the carbohydrate results (GLC).

REACTION MECHANISMS

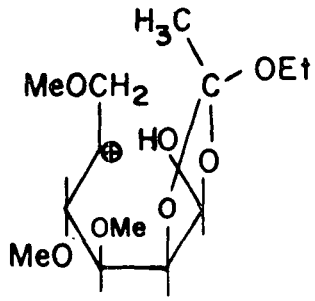
GENERAL

Glycose 1,2-(alkyl orthoacylates) such as 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose can be envisaged as containing both an acetal and an orthoester moiety which have one oxygen atom in common. Thus, any mechanistic discussion of the reactions of glycose 1,2-(alkyl orthoacylates) should include consideration of reactions characteristic of acetals and orthoesters with special attention given to possible reactions which involve the common oxygen, O-1 (24).

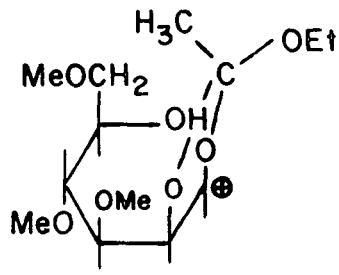
There is considerable evidence that acid-catalyzed hydrolyses and alcoholyses of acetals and orthoesters proceed by carboxonium ions rather than reaction pathways involving bimolecular nucleophilic displacement by water or the alcohol (1,19,23-28). Thus, acid-catalyzed reactions of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose could potentially proceed by protonation of any of the four acetal or orthoester oxygen atoms and subsequent or simultaneous carbon-oxygen bond cleavage to yield an intermediate carboxonium ion (carbonium ions VII and VIII are also considered initially). The possible carbonium ions that could be formed are VII-XIII. Of these ions, VII-IX can be discounted for the following reasons.



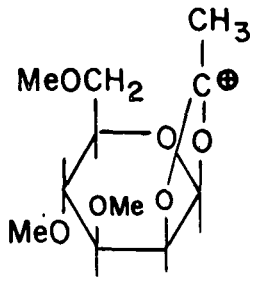
VII



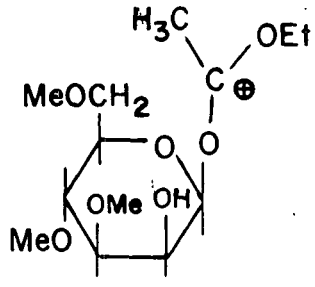
VIII



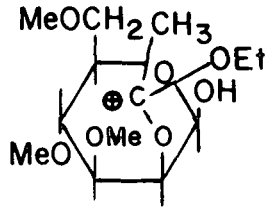
IX



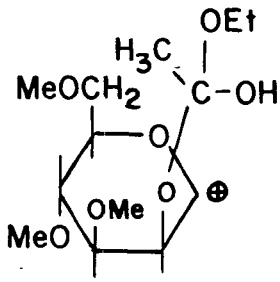
X



XI



XII



XIII

Carbonium ion formation at C-2 (VII) does not occur. If this had occurred, epimeric products would have been formed. Since epimeric products have not been observed previously (1,19,20) or in the present investigation, intermediate VII must not be important.

Reactions involving intermediates VIII and IX are analogous to pathways theoretically possible for acid-catalyzed anomerization or transglycosylation of glycosides (e.g., ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside).

Since the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose is orders of magnitude faster than such reactions (see Results), reactions initiated at the pyranose ring oxygen must not be important.

Of the four remaining carboxonium ions, X-XIII, none can be rigorously excluded as potential intermediates in ethanolysis. However, the potential importance of each of these four intermediates in exo-endo isomerization and in reactions leading to the formation of glycosides and reducing sugar can be evaluated on the basis of the experimental results.

The mechanisms of proton transfer reactions leading to formation of carboxonium ion intermediates in reactions of carbohydrate orthoesters have not been studied previously, or in the present investigation. Therefore, proton transfer reactions are not explicitly included in the mechanisms which will be presented in the following discussion.

EXO-ENDO ISOMERIZATION

The reactions accounting for exo-endo isomerization of the mannose 1,2-(ethyl orthoacetate) undoubtedly involve protonation of an orthoester oxygen followed by or concerted with orthoester carbon-oxygen bond cleavage to yield intermediate carboxonium ions X, XI, and/or XII. Intermediate XIII cannot account directly for exo-endo isomerization since no bond to the asymmetric orthoester carbon is broken.

The potential mechanisms for exo-endo isomerization are shown in Fig. 17. Of the three mechanisms shown, Mechanism A, involving the 1,2-acetoxonium ion X, is the only mechanism involving immediate loss of the ethoxy group in the

formation of the ion. Thus, ethoxy exchange undoubtedly accompanies Mechanism A.[6]

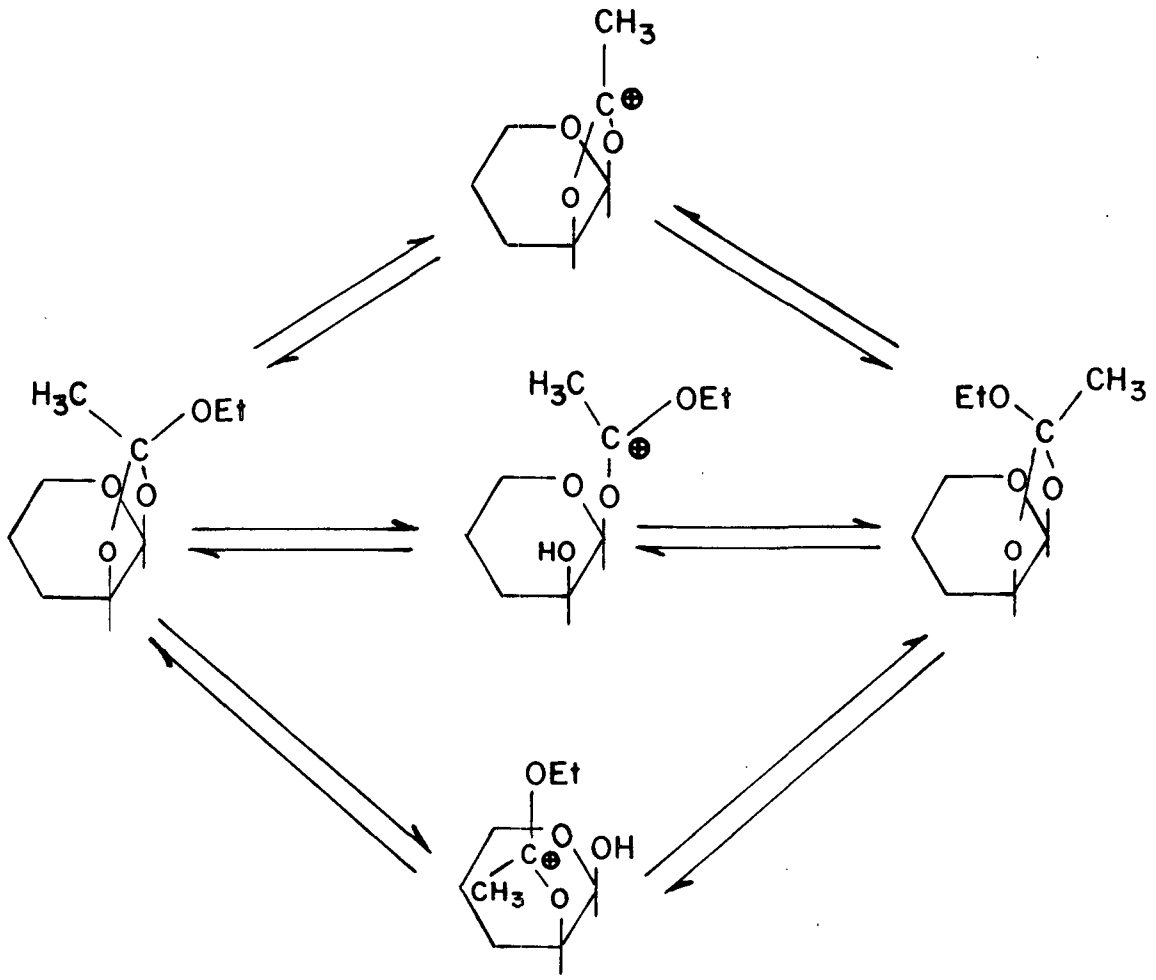


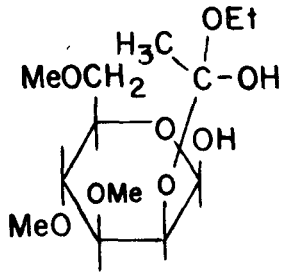
Figure 17. Possible Mechanisms for Exo-Endo Isomerization Initiated by (A) Ethoxy Oxygen Protonation, (B) O-2 Protonation, and (C) O-1 Protonation (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

[6]Ethoxy exchange could also occur by addition of ethanol to either XI or XII, subsequent loss of the original ethanol group, and formation of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose. These mechanisms may be considered as special cases of Mechanisms B and C.

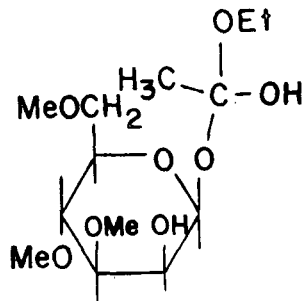
In ethanolysis studies of 1,2-O-[1-(exo-alkoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranoses, it was shown that both exo-endo isomerization and alkoxy exchange were very fast relative to glucose orthoester disappearance (1). It was concluded that the 1,2-acetoxonium ion (analogous to X) was the dominant intermediate in both exo-endo isomerization and alkoxy exchange for ethanolyses of glucose 1,2-(alkyl orthoacetates) (1). Although the mechanism(s) of exo-endo isomerization in the present system was not specifically studied, the data obtained were consistent with the 1,2-acetoxonium ion X being the dominant intermediate in exo-endo isomerization.

In an effort to "trap" the reactive intermediate(s), the acid-catalyzed hydrolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose in 95 mole% ethanol was studied. 2-O-Acetyl- and 1-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose accounted for 93% of the products, and 3,4,6-tri-O-methyl-D-mannopyranose accounted for the remaining 7%.

The reactions of water with intermediate ions XII and XI would be expected to form 2-O-(1-ethoxy-1-hydroxyethyl)- (XIV) and 1-O-(1-ethoxy-1-hydroxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XV), respectively. Intermediates XIV and XV would be expected to yield significant amounts of both 3,4,6-tri-O-methyl-D-mannopyranose and mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose since these intermediates are diesters of carboxylic orthoacids (1,23,24). Thus, the low yield of 3,4,6-tri-O-methyl-D-mannopyranose (7%) suggests that intermediate ions XI (and the mechanism initiated by O-2 protonation) and XII (and the mechanism initiated by O-1 protonation) were only of minor importance in hydrolysis.

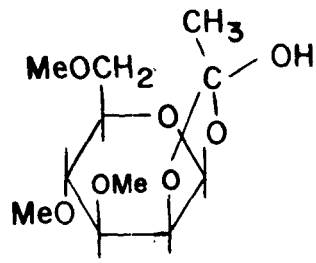


XIV



XV

The reaction of water with the 1,2-acetoxonium ion X would be expected to form the 1,2-O-(1-hydroxyethylidene)-β-D-mannose (XVI). Intermediate XVI would be expected to form only mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose (1,24,29). Thus, the large portion of mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose detected (93%) suggests that intermediate ion X (and the mechanism initiated by protonation of the ethoxy oxygen atom) was very important in hydrolysis.



XVI

In ethanolysis, exo-endo isomerization was relatively fast compared to the formation of glycosides and reducing sugar. If one assumes that the same initial intermediate cations are formed in both ethanolysis (in absolute ethanol) and hydrolysis (in 95 mole% ethanol), the hydrolysis results and the fast rate of exo-endo isomerization relative to other ethanolysis reactions suggest that the 1,2-acetoxonium ion (X) is probably the dominant intermediate ion in exo-endo

isomerization. Nevertheless, the fact that 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose was formed in the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate suggests that Mechanism B and/or C, involving acyclic ions XI and XII, respectively (Fig. 17), must also occur to some degree (see Fig. 23).

FORMATION OF GLYCOSIDES AND REDUCING SUGAR

The mechanisms accounting for the formation of glycosides and reducing sugar and the simultaneous disappearance of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose could potentially involve intermediate carboxonium ions X, XI, XII, and XIII either singly or in combination. Mechanisms involving these intermediates are presented and the potential importance of each mechanism is evaluated on the basis of experimental results. The following list summarizes the experimental results that must be accommodated by the proposed mechanisms.

1. The products detected were:

   (a) Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside,
   (b) Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside,
   (c) Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside,
   (d) Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside,
   (e) 3,4,6-Tri-O-methyl-D-mannopyranose,
   (f) Ethyl acetate, and
   (g) Triethyl orthoacetate.

2. The reaction(s) leading to glycoside formation was highly stereoselective for α-mannopyranosides.

3. In comparing an acid-catalyzed ethanolysis in 0.063N lithium p-toluenesulfonate with an ethanolysis in the absence of salt, the following differences were found (see Table III):

   (a) A larger amount of glycosides (relative to reducing sugar) was formed in the presence of the salt,

   (b) The stereoselectivity for α-mannopyranosides was lower in the presence of lithium p-toluenesulfonate, and

   (c) The reaction was faster in the presence of the salt.

4. Decreasing the initial alcohol concentration (at a constant orthoester concentration) resulted in the following (see Table VI):

   (a) An increase in the formation of glycosides (relative to reducing sugar),

   (b) A decrease in the stereoselectivity of α-mannopyranosides formation, and

   (c) An increase in 2-O-acetyl-glycoside formation relative to 2-hydroxyglycoside formation for reactions in both nitromethane and dichloromethane.

5. The 2-O-acetyl-glycoside:2-hydroxyglycoside ratio was lower in a more polar solvent (at a constant ethanol concentration) (see Table VI).

Initial Protonation at O-1

Mechanism

Protonation at O-1 followed by or concerted with orthoester carbon-O-1 bond cleavage would lead to intermediate ion XII and eventually 3,4,6-tri-O-methyl-D-mannopyranose formation (see Fig. 18); protonation at O-1 followed by or concerted with C-1-O-1 bond cleavage would lead to intermediate ion XIII and eventually glycoside formation (see Fig. 19).

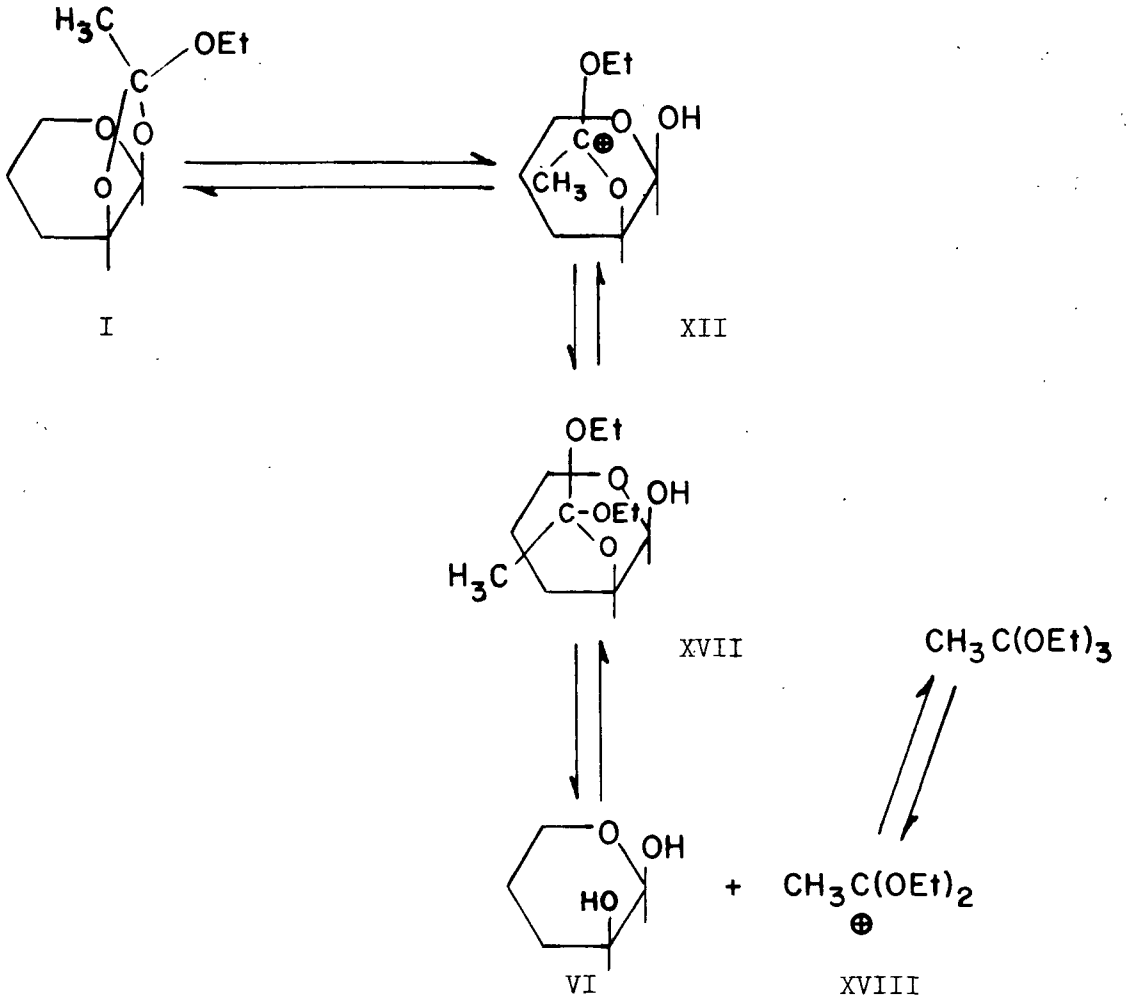


Figure 18. Possible Mechanism for Reducing Sugar Formation Initiated by O-1 Protonation (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

The transition state free energies for the formation of intermediate ions XII and XIII are related to both the ability of the system to delocalize the positive charge developing on the carbon atom (indicated by the stability of the resultant carbonium ion) and the ability of the leaving group to accept the pair of electrons resulting from bond cleavage ("leaving ability"). Relative "leaving abilities" of two species can be roughly correlated with their basicities; the species which is the weaker base would be the better leaving group (23,30). The hydroxylic oxygen atom of XIII, being geminal to two

electronegative oxygen atoms, should be considerably less basic and therefore a better leaving group than the hydroxylic oxygen atom (O-1) of XII, which is geminal to only one oxygen atom. In contrast to the "leaving ability" criterion, the "stable carbonium ion" criterion would favor formation of intermediate ion XII since the positive charge is more delocalized relative to the mannopyranosyl cation XIII. In other words, bond cleavage between O-1 and the orthoester carbon atom utilizes the more stable carbonium ion, whereas O-1-C-1 bond cleavage utilizes the better leaving group. Hence, both C-1-O-1 bond cleavage and orthoester carbon-O-1 bond cleavage might be expected to occur after O-1 protonation.

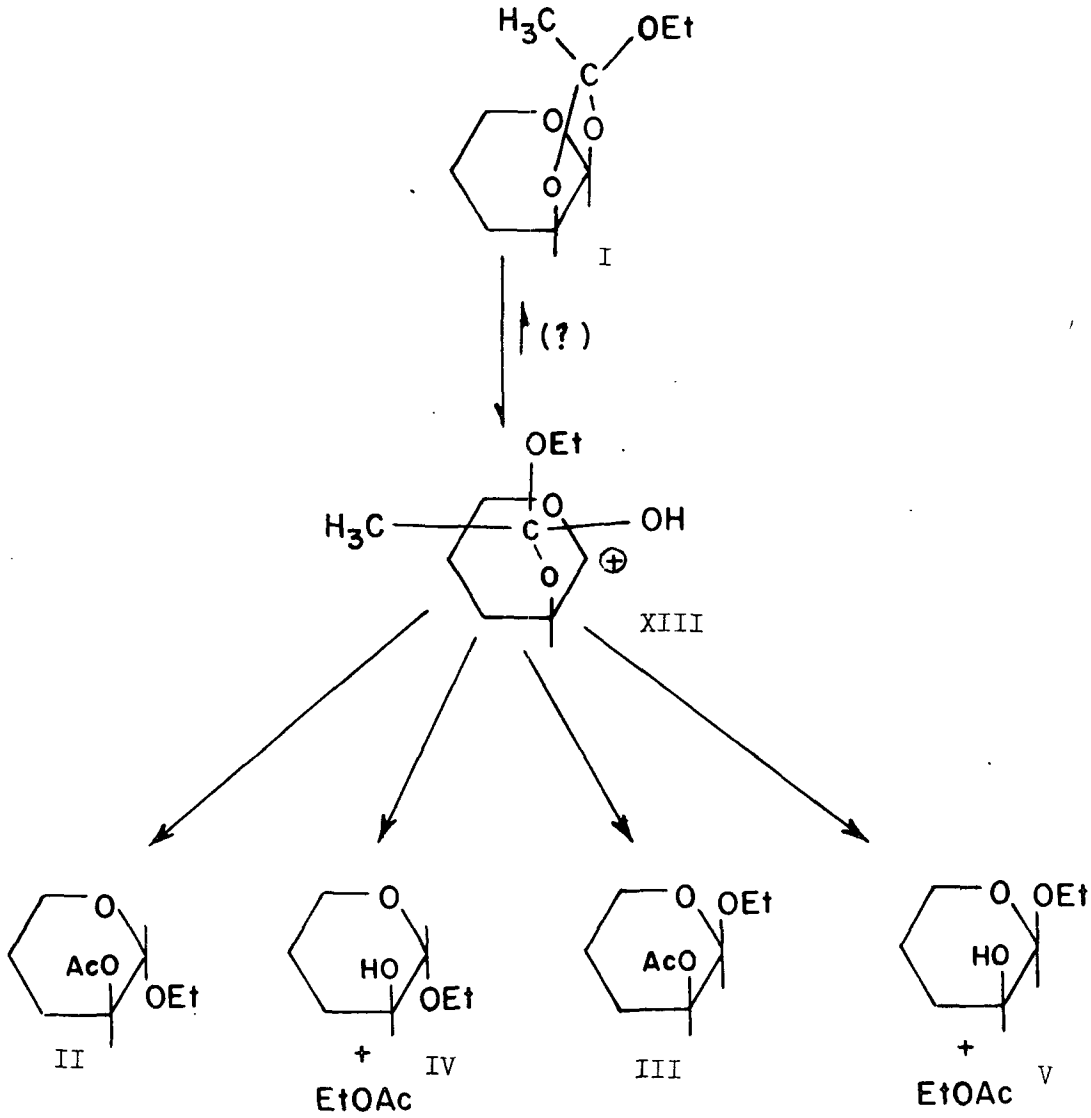


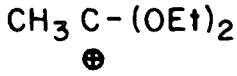
Figure 19. Possible Mechanism for Glycoside Formation Initiated by O-1 Protonation (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

The chronology of glycoside formation from intermediate ion XIII (Fig. 19) is not suggested. Both the C-1 carbonium ion (23) and the 2-O-(1-ethoxy-1-hydroxyethyl) substituent of intermediate ion XIII are expected to be very reactive. Therefore, it is not known whether ester formation from the 2-O-(1-ethoxy-1-hydroxyethyl) substituent would occur before or after ethoxy addition at the C-1 carbonium ion.

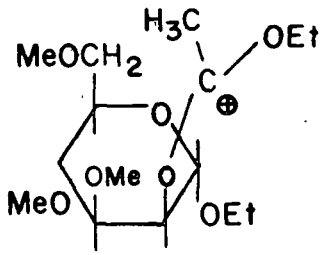
The 2-O-(1-ethoxy-1-hydroxyethyl) substituent of XIII would probably yield both the alkyl acetate and sugar 2-acetate as suggested in Fig. 19 since it is a diester of a carboxylic orthoacid (1,24). However, Perlin (20) has hypothesized that intermediate ions analogous to XIII account for formation of glycosides unsubstituted at C-2 in methanolyses of glycose 1,2-(alkyl orthoacetates), i.e., the 2-O-(1-alkoxy-1-hydroxyethyl) substituent forms the alkyl acetate rather than the sugar 2-acetate. In contrast to this, DeWolfe (19), in a proposed mechanism for hydrolysis of glycose 1,2-(alkyl orthoacylates), has credited this type of substituent with quantitative formation of a 2-O-acyl derivative of the sugar. In an effort to demonstrate that the 2-O-(1-ethoxy-1-hydroxyethyl) substituent yields both the 2-O-acetyl and the 2-hydroxy substituents, the acid-catalyzed hydrolysis of ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside was studied.

Products Derived from *in situ* Generation of a 2-O-(1-Ethoxy-1-hydroxyethyl) Model System

Acid-catalyzed hydrolyses of orthoesters proceed by protonation of an oxygen atom followed by or concerted with cleavage of an orthoester carbon-oxygen bond to yield intermediate carboxonium ions (26). According to this mechanism, the acid-catalyzed hydrolysis of ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside must proceed via one or both of the carboxonium ions shown on the following page.



XVIII



XIX

The hydrolysis of triethyl orthoacetate has been shown to be subject to general acid catalysis (31). In addition, the hydrolytic reactivity of a series of related trialkyl orthocarboxylates was found to closely parallel the estimated basicities of the orthoesters, rather than the relative stabilities of the dialkoxycarbonium ions which presumably are intermediates in their hydrolyses (19). These general observations provide strong support that the rate-limiting step of triethyl orthoacetate hydrolysis involves slow proton transfer which may or may not be concerted with displacement of the 1,1-diethoxyethyl cation.

Based on the similarity of ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside and triethyl orthoacetate, proton transfer to one of the oxygens of the carbohydrate orthoester should be involved in the rate-determining step. Because of the proximity of the electronegative oxygen atoms at C-1 and C-3, the C-2 oxygen atom should be less basic than the ethoxy oxygen atoms. Due to the relative basicities and the fact that there are two ethoxy oxygen atoms and only one C-2 oxygen atom, XIX should be the more important intermediate ion (relative to XVIII) in the hydrolysis of the carbohydrate orthoester.

The observed hydrolysis products, including their solvent dependence, can be accounted for if it is assumed that XIX is the major hydrolysis intermediate ion and that it reacts with water to form XX (see Fig. 20). The following arguments are analogous to those presented previously for acid-catalyzed hydrolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (24).

The hydroxy group of intermediate XX should be relatively acidic because it is geminal to two electronegative oxygen atoms, and hence some ionization to form the conjugate base XXI would be expected (24). Thus, the potential of both intermediates XX and XXI to form observed hydrolysis products, ethyl 2-O-acetyl- and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside, must be considered.

Conjugate bases of diesters of carboxylic orthoacids analogous to XXI are probable intermediates in reversible alkoxide ion-catalyzed transesterification of carboxylic esters (24,32). As shown in Fig. 20, the diester intermediate ion XXI can generate two different carboxylic esters. The ratio of the two esters formed from XXI would depend on the relative "leaving ability" of the two alkoxy groups. As previously suggested, the C-2 oxygen atom should be less basic and hence a better leaving group than the ethoxy oxygen atom. Thus, based on this consideration, XXI should favor ethyl acetate (and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside) formation rather than ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside (and ethanol) formation.

In contrast to the reaction of its conjugate base (XXI), the reaction of XX requires a proton transfer from an acid in the system to either the C-2 oxygen atom or the ethoxy oxygen atom. As previously shown, there is much evidence to suggest that the rate-limiting step in orthoester hydrolysis involves slow proton transfer which may or may not be concerted with displacement

of the carboxonium ion. Presumably, the diester XX reacts via a similar mechanism and, therefore, the relative amounts of ethyl 2-O-acetyl- and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside formed from it will be dictated primarily by the relative basicities of the C-2 oxygen and the ethoxy oxygen atoms. Since the ethoxy oxygen atom should be more basic, the dominant reaction of XX should be protonation of the ethoxy oxygen atom, concerted with or followed by the loss of ethanol and the formation of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

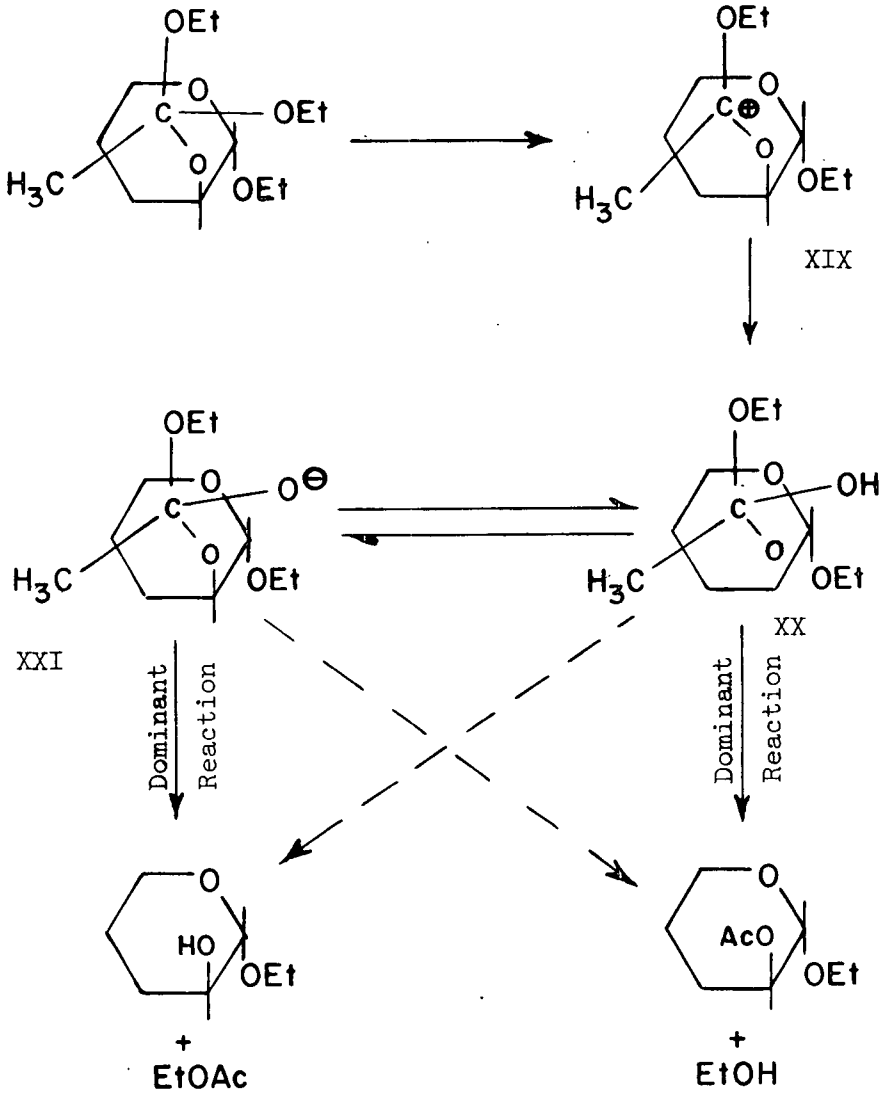


Figure 20. Possible Mechanism for Hydrolysis of Ethyl 2-O-(1,1-Diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

Hence, formation of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside should be favored in reactions of the orthoacid diester XX, whereas reactions of the conjugate base XXI should favor formation of ethyl acetate (and ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside). This predicts that factors which influence the equilibrium between the orthoacid XX and its conjugate base XXI will also affect the product distribution. For example, an increase in the polarity (or basicity) of the reaction solvent would be expected to better stabilize the ionic intermediate XXI, and thus increase the yield of the 2-hydroxyglucoside (ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside). In support of this, it was experimentally found that the amount of unacetylated glycoside (relative to acetylated glycoside) increased as the polarity of the solvent increased (see Table VIII). A mechanism similar to the above accounts for both the solvent dependency and pH dependency of the product distribution of acid-catalyzed hydrolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (24).

The ethyl 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranoside hydrolysis study supports the contention that the 2-O-(1-ethoxy-1-hydroxyethyl) substituent of XIII (Fig. 19) can lead to 2-O-acetyl-glycoside (and ethanol) formation as well as 2-hydroxyglycoside (and ethyl acetate) formation. Results of the hydrolysis study also suggest that the product distribution of acetylated and unacetylated glycosides from reactions of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose with ethanol will be dependent on the polarity and basicity of the solvent if the mechanism outlined in Fig. 19 is important.

Evaluation of the Mechanism

The mechanism involving initial O-1 protonation (see Fig. 18 and 19) can accommodate all of the experimental results with one exception. The one exception, as discussed later, is the fact that decreasing the ethanol concentration of reactions run in nitromethane resulted in an increase in 2-O-acetyl-glycoside formation relative to 2-hydroxyglycoside formation. However, when the mechanism initiated by O-1 protonation and the mechanism initiated by O-2 protonation are considered together, all of the experimental results can be accommodated.

The mechanism initiated by O-1 protonation (see Fig. 18 and 19) can account for all of the products detected. The preferential formation of α-mannopyranosides (relative to β-mannopyranosides) can be explained by the high reactivity of the mannopyranosyl cation (XIII) resulting in reaction with ethanol in most cases before the leaving group is far from the reaction center (23). The decrease in stereoselectivity for α-mannopyranoside formation with increased ionic strength (see Table III) or with decreasing ethanol concentration (see Table VI) can be attributed to enhanced stabilization of the mannopyranosyl cation (XIII). The longer average lifetime of the C-1 carbonium ion allows the leaving group to move farther away from the reaction center before reaction with ethanol occurs. Thus, "shielding" of the β-side of XIII is decreased as stabilization of the mannopyranosyl cation is increased.

Increasing the ionic strength of the reaction solution by adding lithium p-toluenesulfonate would be expected to increase the importance of glycoside formation (relative to reducing sugar formation) as observed (23). Increased ionic strength should stabilize both of the carboxonium ions, XII and XIII. However, in the transition state for formation of XIII, the developing

positive charge is less delocalized than in the transition state leading to XII. The transition state leading to XIII should, therefore, experience more additional stabilization with an increase in ionic strength than the transition state for formation of XII. Thus, the proportion of mannosidic products, which form via XIII, should increase relative to the amount of reducing sugar, which forms via XII, when a salt is added to the system.

The addition of lithium p-toluenesulfonate to the 2,6-dichlorobenzoic acid-catalyzed ethanolysis was found to increase the rate of the reaction by a factor of 4 (see Table III). The addition of a salt to a reaction catalyzed by a weak acid (e.g., 2,6-dichlorobenzoic acid) would be expected to significantly increase the rate of the reaction regardless of the mechanism due to the secondary salt effect (21,33). The activity coefficients of $[H^+]$ and the conjugate base of the acid will decrease with increasing ionic concentration, thus causing an increase in the apparent acid dissociation constant. This increase in the apparent acid dissociation constant leads to an increase in the concentration of protons, thus increasing the rate of the acid-catalyzed reaction.

The mechanism initiated by O-1 protonation (see Fig. 18 and 19) can also account for the increase in glycoside formation observed at lower initial ethanol concentrations in dichloromethane or nitromethane. Carbonium ion XII (Fig. 18) can cyclize to reform the mannose 1,2-(ethyl orthoacetate) (I) or react with ethanol to form 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XVII) which leads ultimately to reducing sugar VI formation. As the ethanol concentration is decreased, the unimolecular reformation of the mannose 1,2-(ethyl orthoacetate) (I) becomes more important relative to the bimolecular formation of intermediate XVII. In comparison with the recyclization of XII, reformation of the mannose 1,2-(ethyl orthoacetate) (I) from XIII (Fig.

19) apparently is less dependent on the ethanol concentration. This characteristic might be expected because of the high reactivity of the 2-O-(1-ethoxy-1-hydroxyethyl) group to form an ester and an alcohol, and of the mannopyranosyl cation to form a glycoside. In summary, at low ethanol concentrations the mannose 1,2-(ethyl orthoacetate) (I) and intermediate ion XII interconvert until C-1-O-1 bond cleavage of the cyclic orthoester occurs to form intermediate ion XIII which leads to glycoside formation. At high ethanol concentrations, the bimolecular reaction of XII with ethanol can occur to form intermediate XVII which leads ultimately to reducing sugar VI formation.

The intermediate ion XIII (Fig. 19) can account for the observed dependency of the acetylated glycoside to unacetylated glycoside ratio on the polarity of the reaction solvent (at constant alcohol concentration) (see Table VI). As previously shown, the acetylated-to-unacetylated glycoside product ratio formed from the 2-O-(1-ethoxy-1-hydroxyethyl) glycoside (XX, Fig. 20) was lower in a more polar solvent (see Table VIII). Thus, a similar intermediate (XIII) should show a similar dependency on the polarity of the reaction solution.

If the mechanism initiated by O-1 protonation (see Fig. 18 and 19) were the only mechanism under consideration, one could suggest that decreasing the ethanol concentration in dichloromethane would account for the increase of 2-O-acetyl-glycoside formation (relative to 2-hydroxyglycoside formation) because of the decrease in polarity of the reaction solution. A similar argument would suggest that decreasing the ethanol concentration in nitromethane should decrease 2-O-acetyl-glycoside formation (relative to 2-hydroxyglycoside formation) because of the increase in polarity of the reaction solution. Contrary to the latter prediction, decreasing the ethanol concentration of reactions run in nitromethane resulted in an increase in 2-O-acetyl-glycoside formation

(relative to 2-hydroxyglycoside formation). As will be shown, this result can be accommodated by the mechanism initiated by O-1 protonation when the mechanism initiated by O-2 protonation is also considered.

Initial Protonation at O-2

Mechanism

Protonation at O-2 followed by or concerted with orthoester carbon-O-2 bond cleavage would result in formation of the carbonium ion XI (see Fig. 21). Reaction of ethanol with XI would form 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XXII). By analogy with the acid-catalyzed ethanolysis of 1-O-(1,1-diethoxyethyl)-2,3,4,6-tetra-O-methyl-α-D-glucopyranose (1,23), the acid-catalyzed ethanolysis of 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XXII) should yield 3,4,6-tri-O-methyl-D-mannopyranose (VI), ethyl 3,4,6-tri-O-methyl-α- (IV) and β-D-mannopyranoside (V).

Evaluation of the Mechanism

The mechanism initiated by O-2 protonation alone (see Fig. 21) cannot accommodate all of the experimental results. However, when this mechanism is considered along with the mechanism initiated by O-1 protonation (see Fig. 18 and 19), all of the observed results can be accommodated.

The mechanism involving initial O-2 protonation will be consistent with some of the experimental results for reasons analogous to those previously presented for the mechanism initiated by O-1 protonation. When these results are discussed, very little detail will be presented to prevent needless repetition.

The mechanism initiated by O-2 protonation can account for all the products detected except for the 2-O-acetyl-glycosides. The preferential formation

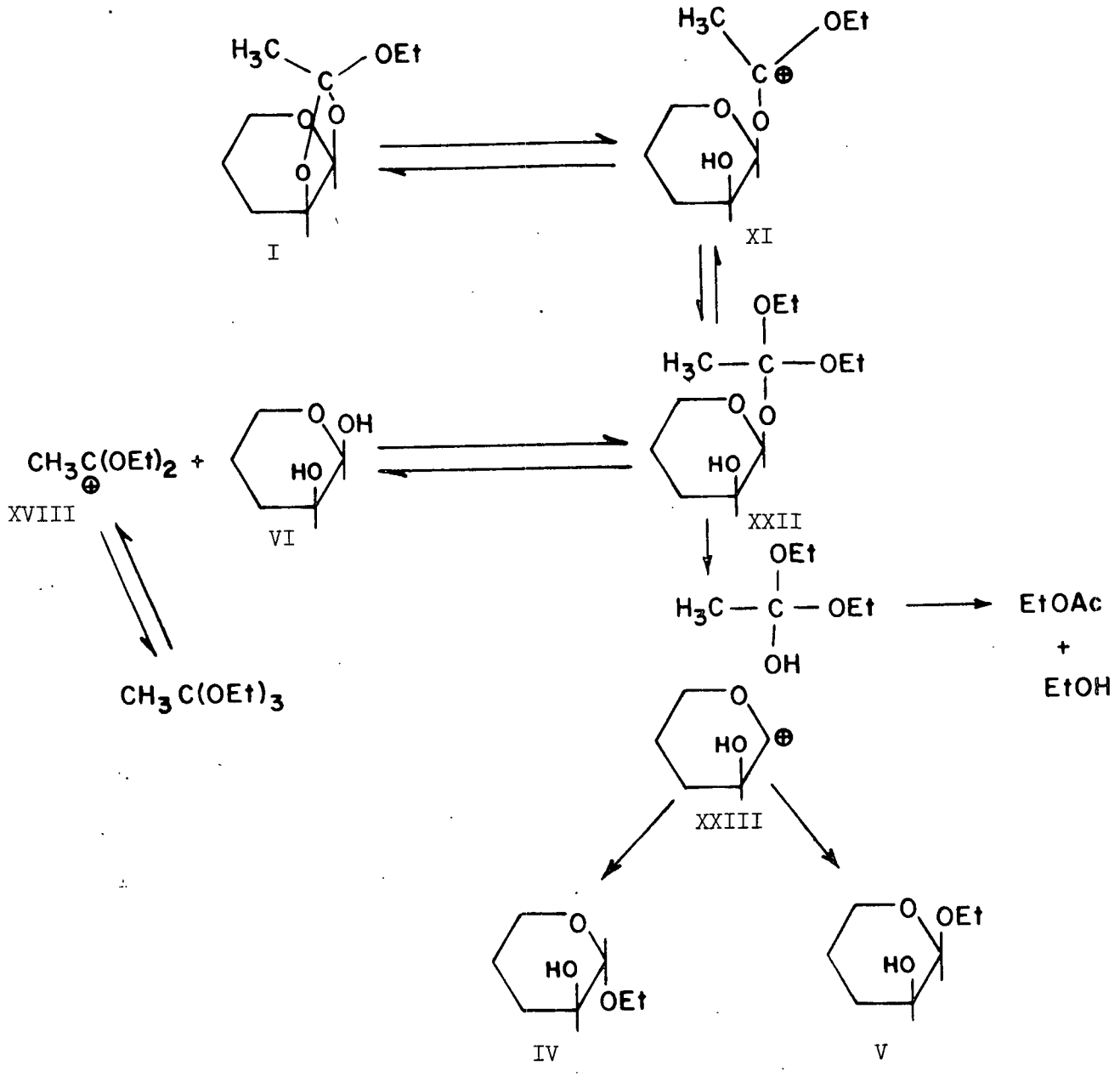


Figure 21. Possible Mechanism for Formation of 2-Hydroxyglycosides and Reducing Sugar Initiated by O-2 Protonation (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

of the α-anomer of the 2-hydroxyglycosides can be explained by the high reactivity of the mannopyranosyl cation XXIII resulting in reaction with ethanol in most cases before the leaving group is far from the reaction center (23). Increasing 2-hydroxyglycoside formation (relative to reducing sugar) upon adding lithium p-toluenesulfonate to an ethanolysis can be attributed to the greater additional stabilization of the intermediate ion XXIII relative to XVIII. This increased stabilization of the C-1 carbonium ion, XXIII, could also account for the decrease in stereoselectivity for 2-hydroxy-α-glycoside formation (relative to 2-hydroxy-β-glycoside formation).

Cation XI (Fig. 21) can either reform the mannose 1,2-(ethyl orthoacetate) (I) or react with ethanol to form 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XXII) which leads ultimately to the formation of reducing sugar (VI) and 2-hydroxyglycosides (IV and V). Decreasing the ethanol concentration should decrease the importance of the reaction of XI with ethanol to form XXII, and thus decrease the formation of 2-hydroxyglycosides and reducing sugar so that at very low ethanol concentrations, this mechanism may not contribute significantly to product formation. However, at high ethanol concentrations, this mechanism must lead to formation of 2-hydroxyglycosides and reducing sugar.

The fact that decreasing the ethanol concentration in nitromethane resulted in an increase in the acetylated-to-unacetylated glycoside ratio can be accounted for only if the mechanism involving initial O-1 protonation and the mechanism involving initial O-2 protonation operate concurrently. As previously discussed, the mechanism involving initial O-1 protonation cannot be the sole explanation for this result. Obviously, the mechanism involving initial O-2 protonation cannot, by itself, explain the results since the mechanism does not account for 2-O-acetyl-glycoside formation.

Decreasing the ethanol concentration of reactions run in nitromethane increase the solvent polarity which would be expected to decrease the acetylated-to-unacetylated glycoside ratio if only the mechanism involving initial O-1 protonation is considered. However, as previously discussed, decreasing the ethanol concentration would be expected to decrease the formation of 2-hydroxyglycosides and reducing sugar formed via the mechanism initiated by O-2 protonation. Such a decrease in 2-hydroxyglycoside formation would increase the acetylated-to-unacetylated glycoside ratio. Thus, the fact that decreasing the ethanol concentration in nitromethane resulted in an increase in the acetylated-to-unacetylated glycoside ratio can be accounted for by a combination of the mechanisms initiated by O-1 or O-2 protonation. Furthermore, a combination of such mechanisms can accommodate all of the experimental results (see Fig. 18, 19 and 21).

Initial Protonation at the Ethoxy Oxygen Atom

Mechanism

The most popular mechanism proposed in the literature (2-4,20,34,35) for the formation of 1,2-trans-2-O-acyl-glycosides from glycose 1,2-(alkyl orthoacylates) involves attack by the alcohol at C-1 of a 1,2-acetoxonium ion (X) (see Fig. 22).

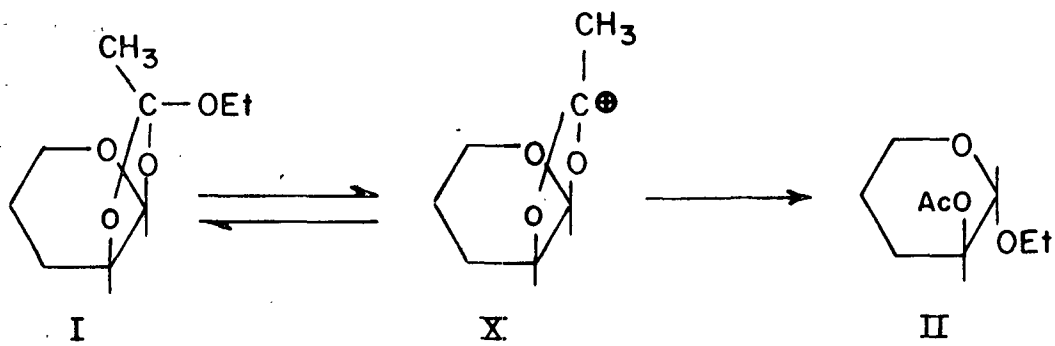


Figure 22. Mechanism Proposed for 1,2-Trans-2-O-acyl Glycoside Formation (2,3) (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

Evaluation of the Mechanism

The mechanism involving initial protonation of the ethoxy oxygen atom (Fig. 22) could account for the high stereoselectivity for the 2-O-acetyl-α-glycoside (relative to the 2-O-acetyl-β-glycoside). However, this mechanism alone cannot account for the effect of changes in the reaction conditions on the product distribution since it accounts for only one product. One might suggest that the mechanism involving initial O-2 protonation (Fig. 21) and the mechanism involving initial ethoxy oxygen atom protonation (Fig. 22) are the only operative mechanisms. This combination could account for all observed products and for the effect of adding lithium p-toluenesulfonate to an ethanolysis as previously discussed if it is assumed that X fragments so that both anomers of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoside could be formed. However, even this combination of mechanisms cannot account for the effects observed when the ethanol concentration was decreased. The experimental results indicate that at an initial alcohol-to-reactant orthoester molar ratio of 2, the reducing sugar (3,4,6-tri-O-methyl-D-mannopyranose) accounted for only 1% of the products (see Table VI). This low yield of reducing sugar suggests that the mechanism initiated by O-2 protonation is relatively unimportant at low ethanol concentrations. Hence, the combination of mechanisms involving initial protonation at either O-2 or the ethoxy oxygen atom (see Fig. 21 and 22) cannot accommodate the significant yields of 2-hydroxyglycosides (29-43%, depending on the inert solvent) detected at low ethanol concentrations. Also, this combination of mechanisms cannot account for the lower ratio of acetylated-to-unacetylated glycosides in nitromethane than in dichloromethane. In fact, on the basis of the mechanism shown in Fig. 22, Kochetkov, et al. (2) predicted that polar solvents would favor formation of the 1,2-trans-2-O-acyl-glycoside, which is contrary to the observed results (see Table VI).

As discussed above, the mechanism involving initial O-2 protonation (Fig. 21) and the mechanism involving initial ethoxy oxygen atom protonation (Fig. 22) cannot be the only operative mechanisms in ethanolysis. As previously discussed, the mechanism involving initial O-1 protonation (Fig. 18 and 19) combined with the mechanism involving initial O-2 protonation can accommodate all the experimental results. Therefore, it follows that these mechanisms (Fig. 18, 19, and 21) combined with the mechanism for glycoside formation initiated by protonation of the ethoxy oxygen atom (Fig. 22) can also accommodate all the experimental results. This fact makes the elimination of the mechanism for glycoside formation outlined in Fig. 22 very difficult, but it is not necessary to invoke this mechanism to account for the observed results. Nevertheless, the maximum importance of this mechanism can be established.

The mechanism involving the 1,2-acetoxonium ion X (Fig. 22) can account for only 1,2-trans-2-O-acyl-glycoside formation. Since this product accounts for only 20% of the ethanolysis products formed in the parallel reactions of the mannose 1,2-(ethyl orthoacetate) (see Table III), the maximum proportion of ethanolysis products formed by this route is 20%. As shown in Table VI, at higher reaction temperatures and at lower initial ethanol concentrations, the relative proportion of the 1,2-trans-2-O-acyl-glycoside increases. Thus, the maximum importance of the mechanism outlined in Fig. 22 is 66% under the reaction conditions studied. However, the mechanism initiated by O-1 protonation and followed by or concerted with C-1-O-1 bond cleavage (Fig. 19) can also account for 1,2-trans-2-O-acyl-glycoside formation. Thus, the importance of the 1,2-acetoxonium ion for the formation of the 1,2-trans-2-O-acyl-glycoside may well be much less than the indicated maximum.

MECHANISM FOR THE ACID-CATALYZED ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

The probable intermediate in acid-catalyzed ethanolysis of 1,1,1-trialkoxyethane is the 1-O-(1,1-diethoxyethyl) cation (27). By analogy, the acid-

$$CH_3C(OEt)_3 \rightleftarrows CH_3\overset{\oplus}{C}(OEt)_2 + EtOH$$

catalyzed transorthoesterification of triethyl orthoacetate with 3,4,6-tri-O-methyl-D-mannopyranose should proceed by addition of a hydroxy group of the reducing sugar to the 1,1-diethoxyethyl cation to form intermediate acyclic carbohydrate orthoesters (see Fig. 23). Intermediates, 2-O-(1,1-diethoxyethyl)- (XVII) and 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XXII), may undergo another transorthoesterification (intramolecular) to form 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I). As suggested in Fig. 23, 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α- (XXV) and β-D-mannopyranose (XXII), and 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I) can undergo ethanolysis to form glycosides (1,23). The mechanisms for ethanolysis product formation from the mannose 1,2-(ethyl orthoacetate) have been previously discussed. The mechanisms for ethyl 3,4,6-tri-O-methyl-α- (IV) and β-D-mannopyranoside (V) formation from the ethanolysis of the acyclic orthoesters (XXII and XXV) are analogous to the mechanism shown for the ethanolysis of 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose (XXII) in Fig. 21.

The detection of the 2-O-acetyl-glycoside (II) is good evidence that the mannose 1,2-(ethyl orthoacetate) (I) was formed in the reaction, since no other expected intermediate orthoester can account for this product. If the

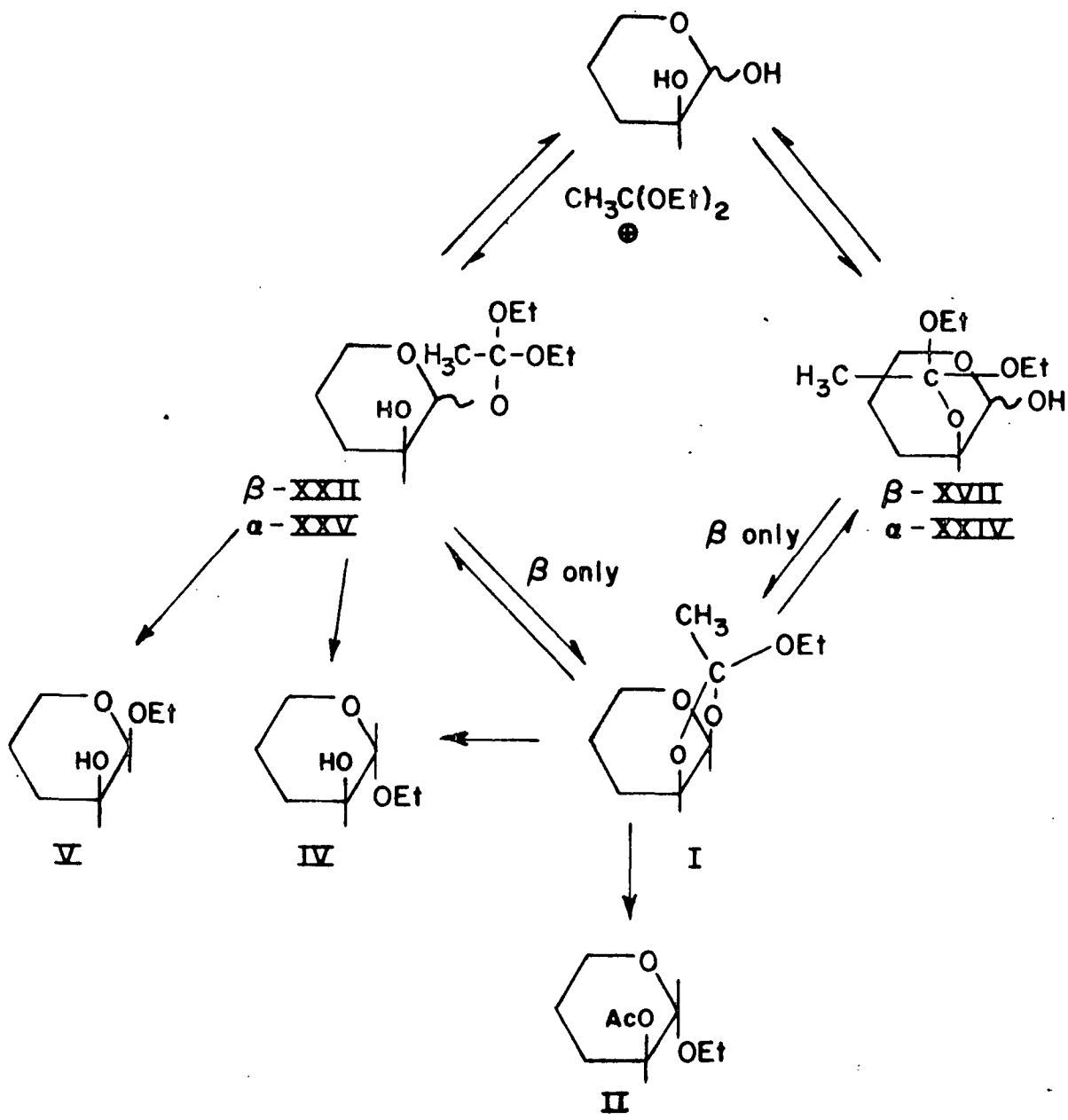


Figure 23. Possible Mechanism for the Acid-Catalyzed Ethanolysis of 3,4,6-Tri-O-methyl-D-mannopyranose in the Presence of Triethyl Orthoacetate (the 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown)

mannose 1,2-(ethyl orthoacetate) (I) was the only intermediate leading to glycoside formation, the product distribution of glycosides for the ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose (VI) in the presence of triethyl orthoacetate should be very similar to that observed for the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose (I). The glycoside product distributions were, however, significantly different. This difference suggests that the acyclic orthoester intermediates XXII and XXV can form 2-hydroxyglycosides without first forming the cyclic orthoester (I).

COMPARISON OF ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE WITH THAT OF THE ANALOGOUS α-D-GLUCOPYRANOSE ORTHOESTER

The mechanisms proposed for the ethanolysis of 1,2-O-[1-(exo-ethoxy)-ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranose (1) can accommodate the experimental results for the ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. The product distributions and rate constants, however, differ for the two reactions. As shown in Table IX the specific pseudo first-order rate constant (k_r) for the 0.005N 2,6-dichlorobenzoic acid-catalyzed ethanolysis of the methylated glucose 1,2-(ethyl orthoacetate) was approximately five times that for the analogous mannose system. This difference in rate constants corresponds to a difference in free energies of activation of only 0.98 kcal $mole^{-1}$.[7] The data in Table IX also show that the ethanolysis of the methylated mannose 1,2-(ethyl orthoacetate) yielded 33% glycosides (and 67% reducing sugar) compared to 79% (and 21%) for the analogous glucose system. Similar differences in rate constants and product distributions have been noted for methanolyses of acetylated glucose and mannose 1,2-(alkyl orthoacetates) (20).

[7] Assuming that the ratio of the pseudo first-order rate constants equals that of the true rate constants of the rate-controlling steps.

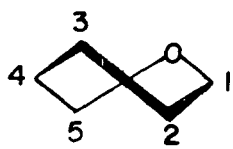
TABLE IX

2,6-DICHLOROBENZOIC ACID (0.005N)-CATALYZED ETHANOLYSES OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-D-GLYCOPYRANOSES (0.068M) AT 25.0°C

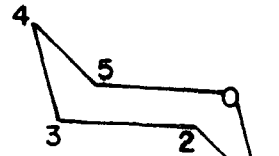
	Orthoester	
	Mannose	Glucose[a]
Product, mole fraction		
Reducing sugar	0.675	0.209
1,2-Trans-2-O-acetyl-glycoside	0.178	0.196
1,2-Trans-2-hydroxyglycoside	0.148	0.571
1,2-Cis-2-hydroxyglycoside	0.0	0.028
Specific rate constant, 10^5 k_r, sec^{-1}	0.66	3.43

[a] Data from Reference (1).

The reason for the differences in rate constants and product distributions for the two systems is not readily apparent. Differences between the glucose and mannose 1,2-(ethyl orthoacetates) include the configurations at C-1 and at C-2 and the conformations of the pyranoid rings. NMR analysis, in conjunction with crystallographic analysis, indicates that the pyranoid ring of 3,4,6-tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-α-D-glucopyranose (in $CDCl_3$) exists in a $^0S_2$ ($^3S_5$) conformation (14). As suggested on the basis of NMR coupling constants (Appendix VIII), the pyranoid ring of 3,4,6-tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-β-D-mannopyranose (in $CDCl_3$) exists in a slightly distorted $^4C_1$ conformation. Presumably, the methylated glycose



$^0S_2$ ($^3S_5$)



$^4C_1$

1,2-(ethyl orthoacetates) (in ethanol) exist in conformations similar to their analogous acetylated derivatives (in $CDCl_3$). Thus, there are several structural differences between the methylated mannose and glucose 1,2-(ethyl orthoacetates). Unfortunately, the differences in reactivity and product distributions for ethanolyses of the respective glycose 1,2-(ethyl orthoacetates) cannot be correlated with specific structural differences.

CONCLUSIONS

Glycoside formation and reversible transorthoesterifications are the only types of reactions that occur in acid-catalyzed ethanolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. In acid-catalyzed ethanolysis, the mannose 1,2-(ethyl orthoacetate) forms ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (and ethyl acetate), and 3,4,6-tri-O-methyl-D-mannopyranose (and triethyl orthoacetate) in parallel first-order reactions. 3,4,6-Tri-O-methyl-D-mannopyranose, triethyl orthoacetate, and ethanol subsequently react to form ethyl 3,4,6-tri-O-methyl-α- and β-D-mannopyranoside, and 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose in parallel reactions. These latter reactions exhibit first-order kinetic dependence on both the reducing sugar and triethyl orthoacetate.

The mechanisms previously proposed for acid-catalyzed ethanolyses of 1,2-O-[1-(exo-alkoxy)ethylidene]-3,4,6-tri-O-methyl-α-D-glucopyranoses (1) can accommodate the experimental results observed for the ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. In addition, these mechanisms appear to be valid for reactions run in inert solvents and at various alcohol concentrations.

The dominant mechanism for exo-endo isomerization of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose, which is fast relative to glycoside formation, involves alkoxy exchange via the 1,2-acetoxonium ion. However, other reaction pathways for exo-endo isomerization were shown to be operative to some extent.

Two similar mechanisms collectively explain the formation of glycosides under ethanolysis conditions. These mechanisms involve the formation of a carbonium ion at C-1 of the sugar concurrently with the formation of a diester of an orthoacid. This occurs either (1) as the initial step or (2) subsequent to transorthoesterification to form 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose. Ethanol reacts at the C-1 carbonium ion to form α- and β-glycosides and the diester of the orthoacid forms a carboxylic ester and an alcohol. As the ethanol concentration decreases, initial formation of a carbonium ion at C-1 increases relative to initial transorthoesterification to form the 1-O-(1,1-diethoxyethyl) derivative. Although the 1,2-acetoxonium ion cannot be excluded as an important intermediate in glycoside formation, the experimental results can be accommodated without invoking this mechanism.

The 2-O-(1-ethoxy-1-hydroxyethyl) substituent, formed when carbonium ion formation at C-1 is the initial step in glycoside formation, can yield either the 2-O-acetyl substituent (and ethanol) or the 2-hydroxy substituent (and ethyl acetate). The proposed mechanism is consistent with the observation that formation of the 2-O-acetyl substituent decreases (relative to the formation of the 2-hydroxy substituent) as the polarity of the solvent increases (at constant alcohol concentrations).

The mechanisms accounting for 3,4,6-tri-O-methyl-D-mannopyranose (and triethyl orthoacetate) formation involve two successive transorthoesterification steps in which only the order of bond cleavage is different. The importance of product formation by these mechanisms (relative to glycoside formation by other mechanisms) decreases as the ethanol concentration decreases.

EXPERIMENTAL

GENERAL ANALYTICAL PROCEDURES

Melting points were determined on a Thomas Hoover capillary apparatus.

Elemental analyses were performed by Chemalytics, Inc., 2330 S. Industrial Park Dr., Tempe, Arizona.

Optical rotations were measured on a Perkin-Elmer 141 MC polarimeter.

The 220-MHz nuclear magnetic resonance (NMR) spectrum of 3,4,6-tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-β-D-mannopyranose was determined by Morgan Schaffer Corporation, 5110 Courtrai Avenue, Montreal 252, Quebec, Canada. All other NMR spectra were determined with a Varian A-60A spectrometer at the normal probe temperature (40°C) using tetramethylsilane as an internal standard.

Thin-layer chromatography (TLC) was performed on microscope slides coated with either silica gel G or aluminum oxide G. Spot visualization was accomplished by spraying the TLC plates with methanolic sulfuric acid (20%, v/v) and heating.

Gas-liquid chromatographic (GLC) analyses were made on a Varian Aerograph 1200-1 instrument equipped with a hydrogen flame ionization detector and a Honeywell Electronic 16 recorder equipped with a disc chart integrator. Prepurified nitrogen was used as the carrier gas. All columns were housed in 0.125-inch o.d. stainless steel tubing. The conditions used are listed below:

Conditions A: Column, 5% SE 52 on 60/80-mesh A/W DMCS Chrom. W (10 ft); N_2 flow rate, 30 ml/min; column temperature, 170°C for 19 min, 170-210°C at 4°C min^{-1}; injector temperature, 255°C; detector temperature, 265°C.

Conditions B: Column, 80/100-mesh Porapak (5 ft); N_2 flow rate, 20 ml/min; column temperature, 100-165°C at 2°C min^{-1}; injector temperature, 180°C; detector temperature, 265°C.

REAGENT PREPARATION AND/OR PURIFICATION

Chloroform (36), cyclohexanol (37), ethanol (1,38), picric acid (1), propanoic anhydride (1,39), and triethylamine (39) were purified according to published procedures. Ethanol used in kinetic runs was subjected to the purification procedure twice; the second time just prior to the kinetic run.

2,6-Lutidine (Eastman Organic Chemical, practical grade) and triethyl orthoacetate (Aldrich Chemical Co., Inc.; 97%) were fractionally distilled (40-cm Vigreux column). Nitromethane was purified by percolating it through Drierite, followed by fractional distillation (40-cm Vigreux column) (39,40).

2,6-Dichlorobenzoic acid (1,41) and lithium p-toluenesulfonate (1) were prepared and purified by D. P. Hultman according to published procedures.

PREPARATION OF COMPOUNDS AND PROOF OF STRUCTURE

3,4,6-TRI-O-ACETYL-1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-β-D-MANNOPYRANOSE

D-Mannose (100 g) was acetylated with cold (0°C) acetic anhydride (500 ml) and pyridine (650 ml) (42) to yield penta-O-acetyl-D-mannopyranose as an oil (215 g). The oil in 1,2-dichloroethane (300 ml) was allowed to react with hydrobromic acid in glacial acetic acid (200 ml, 36% HBr) for 2 hr, diluted with chloroform (450 ml), and washed with water (500 ml). The aqueous phase was back-extracted with chloroform (450 ml). The combined chloroform phases were washed with ice water (600 ml), 5% sodium bicarbonate (600 ml), and ice water (600 ml); dried (Na_2SO_4); and concentrated *in vacuo* to yield crude 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl bromide (218 g) as an oil.

The above oil (218 g), 2,6-lutidine (85 ml), and anhydrous ethanol (65 ml) in chloroform (700 ml) were refluxed for 1 hr, allowed to cool, washed with ice water (3 × 800 ml), dried (Na_2SO_4), and concentrated *in vacuo* to an oil. The oil was crystallized from isopropyl ether (160 ml) containing a trace of pyridine to yield the title compound (131 g, 63% based on D-mannose). Several recrystallizations of the product from isopropyl ether-ethanol (3:1, v/v) containing a trace of pyridine gave a pure compound: m.p. 103-104°C, $[\alpha]_D$ -16.5 (*c* 2.2, $CHCl_3$) (found: C, 51.0; H, 6.3%. $C_{16}H_{24}O_{10}$ requires C, 51.1; H, 6.4%); NMR (220 MHz) δ ($CDCl_3$) 1.74 (3H, *s*, *endo*-CH_3-C); 5.51 (1H, *d*, H-1, $J_{1,2}$ 2.5 Hz), 4.61 (H, *m*, H-2, $J_{2,3}$ 4.0 Hz), 5.18 (1H, *m*, H-3, $J_{3,4}$ 10.0 Hz), 5.31 (1H, *m*, H-4, $J_{4,5}$ 9.75 Hz), 3.71 (1H, *m*, H-5, $J_{5,6a}$ 3 Hz, $J_{5,6b}$ 5 Hz), 4.16 (1H, *m*, H-6a, $J_{6a,6b}$ 12 Hz), 4.24 (1H, *m*, H-6b), 2.05, 2.06, 2.11 (3 × AcO), 3.57 (2H, *m*, OCH_2CH_3), and 1.17 ppm (3H, OCH_2CH_3). Analysis of the spectrum was based on simplified *ABX* analyses for the systems H-4, H-3, H-2; H-4, H-3, H-5; and H-6a, H-6b, H-5 since in all of the systems γ_{AB}>10 Hz (*43*).

Previously, preparations of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose were reported to have: m.p. 102.5-104°C, $[\alpha]_D^{20}$ -15° ($CHCl_3$) (*44*) and m.p. 81-82°C, $[\alpha]_D$ -28° ($CHCl_3$) (*19*,*45*).

1,2-*O*-[1-(*EXO*-ETHOXY)ETHYLIDENE]-3,4,6-TRI-*O*-METHYL-β-D-MANNOPYRANOSE (I)

The method of preparation is analogous to that used by Hultman (*1*) for the preparation of 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-α-D-glucopyranose. Powdered sodium hydroxide (150-160 g) and 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-β-D-mannopyranose (50 g) were added to tetrahydrofuran (800 ml) in a 3000-ml three-necked, round-bottom flask fitted with a dropping funnel and an efficient stirrer, and maintained in a water bath at

24-28°C. Dimethyl sulfate (81 ml) was added dropwise during 3 hr to the vigorously stirred mixture. After an additional 3 hr, triethylamine (250 ml), benzene (580 ml), and enough water to dissolve all solids were added to the flask. The mixture was heated (60°C) for 1 hr with stirring. After cooling, the usually encountered three-phase (liquid) system was broken by adding water and benzene. The organic phase was washed with 1% aqueous potassium iodide (1 × 500 ml), 1% aqueous sodium thiosulfate (1 × 500 ml), and water (2 × 500 ml). The aqueous phases were extracted with chloroform and the organic extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo* to an oil (34.9 g, 90% yield).

Fractional distillation of the oil from powdered barium oxide (2 g) under reduced pressure (0.05-mm Hg) gave 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose: $[\alpha]_D$ -2.6° (*c* 3.2, $CHCl_3$) (found: C, 53.2; H, 8.1. $C_{13}H_{24}O_7$ requires C, 53.4; H, 8.3%).

Prolonged acid hydrolysis of the product gave known 3,4,6-tri-*O*-methyl-α-D-mannopyranose, thus demonstrating the 3,4,6-tri-*O*-methyl substitution of the title compound. The stability of the 1,2-*O*-[1-(*exo*-ethoxy)ethylidene] group during methylation and subsequent work-up was readily demonstrated by comparison of NMR data before and after methylation: before methylation, δ($CDCl_3$) 1.74 (3H, *s*, *endo*-CH_3-C), 5.51 (1H, *d*, H-1, $J_{1,2}$ 2.5 Hz), and 4.61 ppm (1H, *m*, H-2, $J_{2,3}$ 4.0 Hz); after methylation, δ($CDCl_3$) 1.72 (3H, *s*, *endo*-CH_3-C), 5.41 (1H, *d*, H-1, $J_{1,2}$ 2.5 Hz), and 4.57 ppm (1H, *t*, H-2, $J_{2,3}$ 2.5 Hz).

3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSE (VI)

Crude 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (24 g) was refluxed with 0.2N sulfuric acid (200 ml) for 18 hr. The solution was allowed to cool, deionized with Amberlite MB-3 (H^+, OH^-) resin and concentrated in vacuo to a colorless oil. The oil was crystallized from ethyl ether-ethanol (4:1; v/v) to yield 13.2 g (72% yield) of material, m.p. 102-107°C. Several recrystallizations from ethyl ether-ethanol (3:1; v/v) yielded a pure compound: m.p. 107-108°C; $[\alpha]_D$ + 20.7° → +8.6° (c 1.2, H_2O); NMR δ($CDCl_3$) 5.22 (1H, m, H-1; collapses to two doublets, 5.20 and 5.45 on D_2O addition), 4.03 (1H, m, H-2), 3.52 (6H, 2 × MeO), 3.40 (3H, 1 × MeO), 4.85 (1H, d, OH exchanged with D_2O), and 3.14 ppm (1H, d, OH exchanged with D_2O). Literature (46): m.p. 104-106°C; $[\alpha]_D$ +20° → +8° (c 0.9, H_2O).

1,2-DI-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSE

Crystalline 3,4,6-tri-O-methyl-α-D-mannopyranose (4.7 g) was dissolved in cold (-7°C) acetic anhydride (30 ml) and pyridine (60 ml). After 30 hr at -7°C, the acetic anhydride-pyridine solution was added to vigorously stirred ice water (500 ml). After being stirred for 30 min, the aqueous solution was extracted with chloroform (3 × 100 ml), washed with 1N hydrochloric acid (1 × 200 ml), saturated aqueous sodium bicarbonate (1 × 250 ml), and ice water (1 × 250 ml). The chloroform solution was concentrated in vacuo to an oil. The oil was crystallized from isopropyl ether to give 5.66 g (87% yield) of product. Several recrystallizations gave a pure compound: m.p. 57-58°C; $[\alpha]_D^{22}$ +61.5 (c 1.8, $CHCl_3$) (found: C, 51.0; H, 7.2. $C_{13}H_{22}O_8$ requires C, 51.0; H, 7.2%); NMR δ($CDCl_3$) 6.10 (1H, d, H-1, $J_{1,2}$ 2.0 Hz), 5.30 (1H, m, H-2), 3.44, 3.46, and 3.58 (3 × MeO), 2.11 and 2.16 ppm (2 × AcO).

Lemieux, et al. (47) found that the anomeric proton resonated at δ($CDCl_3$) 6.1 for penta-O-acetyl-α-D-mannopyranose and at 5.7 ppm for penta-O-acetyl-β-D-mannopyranose. Therefore, the chemical shift for the anomeric proton was consistent with the assigned structure. The α configuration was also confirmed by the high, positive optical rotation, $[\alpha]_D$ +61.5° (c 1.8, $CHCl_3$).

1,2-DI-O-ACETYL-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE

Crude 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (22.3 g) was dissolved in 0.005N sulfuric acid (200 ml). After 4 minutes at room temperature, the solution was neutralized with sodium bicarbonate, and extracted repeatedly with chloroform (5 × 100 ml). The chloroform solution was concentrated in vacuo to an oil. The oil was acetylated with cold (-7°C) acetic anhydride (40 ml) and pyridine (80 ml). After 30 hr at -7°C, the acetic anhydride-pyridine solution was worked up by the same procedure described for 1,2-di-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranose. The oil obtained was crystallized from isopropyl ether to give 10.1 g (43% yield). Physical constants after recrystallization were: m.p. 99-100°C; $[\alpha]_D^{22}$ -24.5 (c 1.9, $CHCl_3$) (found: C, 51.3; H, 7.3. $C_{13}H_{22}O_8$ requires C, 51.0; H, 7.2%); NMR δ($CDCl_3$) 5.74 (1H, H-1), 5.56 (1H, H-2), 3.43 (2 × MeO), 3.55 (1 × MeO), 2.07 and 2.16 ppm (2 × AcO).

ETHYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSIDE (II)

Anhydrous ethanol (200 ml) and acetyl chloride (2 ml) were added to crude 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (25.1 g), and the solution was refluxed for 12 hr. Aqueous sodium hydroxide (1.0N, 200 ml) was added and the resulting solution was refluxed for 2 hr, cooled, and sulfuric acid was added to lower the pH to ca. 8. The dark-brown solution was

treated with carbon, filtered through Celite, and concentrated *in vacuo*. The concentrate was dissolved in hot chloroform (500 ml), filtered to remove the insoluble salts, and concentrated *in vacuo* to a yellow oil (20.7 g). A solution of pyridine (80 ml) and acetic anhydride (40 ml) was added to the oil. After 16 hr at room temperature, the acetylation solution was poured into 1000 ml of ice water. After stirring 30 minutes, the product was extracted with chloroform (2 × 250 ml), and the combined chloroform extracts were washed with 1*N* hydrochloric acid(500 ml), saturated aqueous sodium bicarbonate (500 ml), and water (500 ml). The solution was concentrated to an oil which crystallized from isopropyl ether; two recrystallizations from isopropyl ether gave 11.7 g (46.5% yield) of the pure compound; m.p. 72-73°C, $[\alpha]_D^{22}$ +49.5° (*c* 2.5, $CHCl_3$) (found: C, 53.4; H, 8.1. $C_{23}H_{24}O_7$ requires C, 53.4; H, 8.3%); NMR $\delta(CDCl_3)$ 4.82 (1H, *d*, H-1, $J_{1,2}$ 1.8 Hz), 5.27 (1H, H-2), 2.13 (3H, *s*, OAc), and 1.21 ppm (3H, *t*, $OCH_2\underline{CH_3}$).

ETHYL 3,4,6-TRI-*O*-METHYL-α-D-MANNOPYRANOSIDE (IV)

Ethyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-mannopyranoside (14.0 g) was dissolved in methanol (200 ml). Sodium methoxide (0.5*N*, 8 ml) in methanol was added to the solution. After three days at room temperature, the solution was neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated *in vacuo* to an oil (yield, 12.0 g; 100%).

The oil was purified by distillation at reduced pressure (0.3-mm Hg, b.p. 110°C) through a 7-inch Vigreux column. The distillate, $[\alpha]_D^{22}$ +82.1° (*c* 2.0, $CHCl_3$), was stored in a desiccator over sodium hydroxide pellets (found: C, 52.8; H, 8.7. $C_{11}H_{22}O_6$ requires C, 52.8; H, 8.9%); NMR $\delta(CDCl_3)$ 4.86 (1H, *d*, H-1, $J_{1,2}$ 1.5 Hz), 1.20 (3H, *t*, $OCH_2\underline{CH_3}$), and 3.15 ppm (1H, *s*, OH-2).

ETHYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSIDE (III)

3,4,6-Tri-O-methyl-α-D-mannopyranose (12.0 g) was dissolved in triethyl orthoacetate (60 ml) and ethanol (320 ml). The reaction was monitored by TLC (silica gel; chloroform-ethanol, 10:1, v/v) and acetyl chloride (0.3 ml) was added daily until the starting material was consumed (10 days). Water (ca. 200 ml) was added to hydrolyze residual triethyl orthoacetate, and the solution was concentrated in vacuo to ca. 400 ml. Aqueous sodium hydroxide (0.2N, 200 ml) was added, and the resulting solution was refluxed for 3 hr. The solution was neutralized with sulfuric acid to pH ca. 8, treated with carbon, filtered through Celite, and concentrated in vacuo. The residue was dissolved in hot chloroform, filtered to remove the insoluble salts, and concentrated in vacuo to an oil (12.2 g).

The oil was acetylated with acetic anhydride (25 ml) and pyridine (50 ml) overnight, and worked up in the usual manner. The yellow oil obtained was crystallized from isopropyl ether (10 ml of solvent per g of oil). TLC (silica gel; chloroform-ethyl acetate, 5:2, v/v) indicated that the first crystals isolated were ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside. Using these crystals as seed, a total of 2.16 g (14% yield) of the title compound was obtained by selective crystallization. In addition, 7.4 g of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoside (predominantly α) was obtained. The physical constants of the title compound were: m.p. 96-97°C, $[\alpha]_D^{27}$ -71.5° (c 1.4, $CHCl_3$) (found: C, 53.4; H, 8.4. $C_{13}H_{24}O_7$ requires C, 53.4; H, 8.3%); NMR δ($CDCl_3$) 4.50 (1H, d, H-1, $J_{1,2}$ 1.5 Hz), 5.53 (1H, H-2), 2.13 (3H, s, OAc), and 1.20 ppm (3H, t, $OCH_2\underline{CH_3}$).

ETHYL 3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSIDE (V)

Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside (2.35 g) was dissolved in methanol (30 ml). Sodium methoxide (1N, 1.5 ml) in methanol was added, and after 48 hr the solution was neutralized with Amberlite IR-120 (H^+) resin. The solution was concentrated *in vacuo* to an oil (100% yield) which crystallized from isopropyl ether. Several recrystallizations gave the title compound: m.p. 62.5-64.0°C, $[\alpha]_D^{27}$ -79.6° (*c* 1.1, $CHCl_3$) (found: C, 52.7; H, 8.9. $C_{11}H_{22}O_8$ requires C, 52.8; H, 8.9%); NMR δ($CDCl_3$) 4.42 (1H, *d*, $J_{1,2}$ 1.5 Hz), 1.25 (3H, *t*, $OCH_2\underline{CH_3}$), and 2.32 ppm (1H, *s*, OH-2).

ETHYL 2-O-(1,1-DIETHOXYETHYL)-3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSIDE

The following procedure is analogous to that used by Hultman, *et al.* (23) for the preparation of 1-O-(1,1-diethoxyethyl)-2,3,4,6-tetra-O-methyl-α-D-glucopyranose. Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (5.8 g), triethyl orthoacetate (50 ml), and 2,6-dichlorobenzoic acid (0.5 g) were heated at reduced pressure (125-mm Hg, protected from water vapor) in a Kontes short-path still fitted with a 7-inch Vigreux column. The use of a magnetic stirrer prevented bumping during distillation. In a total time of 30 minutes, the following distillates were collected: 1.4 ml (head temperature 41-62°C); 2 ml (head temperature 73-80°C). The reaction mixture was allowed to cool, diluted with absolute chloroform (100 ml) containing triethylamine (10 ml), washed with ice-cold 0.1N sodium hydroxide (2 × 100 ml) and ice-cold water (100 ml); dried (Na_2SO_4), and concentrated *in vacuo* to a yellow oil.

The NMR spectrum (see Fig. 11) was consistent with the title compound: δ($CDCl_3$) 1.48 (*s*, CH_3-C), 1.20 (*m*, $OCH_2\underline{CH_3}$), and 4.97 ppm (*d*, H-1). The NMR spectrum indicated that residual triethyl orthoacetate (*ca.* 15% by weight)

was present, but there was no evidence for either ethyl 2-O-acetyl- or ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

Attempts to purify the oil by dry column chromatography on alumina (both neutral and basic Al_2O_3 were tried; elution with isopropyl ether-pyridine, 10:1, v/v) and distillation failed. Analyses of the resulting samples indicated that hydrolysis had occurred during each of the attempted purification procedures.

CYCLOHEXYL 3,4,6-TRI-O-METHYL-β-D-GLUCOPYRANOSIDE·

1,2-Di-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (22.9 g) (1) was shaken with hydrogen bromide (21 g) in 1,2-dichloromethane (250 ml) (40). After 30 minutes, the solution was poured into rapidly stirred ice water (1000 ml). After 10 minutes, the aqueous solution was extracted with chloroform (3 × 200 ml). The combined chloroform extracts were washed with saturated sodium bicarbonate (500 ml) and water (500 ml), dried (Na_2SO_4), and concentrated *in vacuo* to crude 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

Crude 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide was stirred with purified cyclohexanol (25 ml) in a Koenigs-Knorr reaction vessel employing cadmium carbonate (9.7 g) and Drierite (70 g, powdered) in dry toluene (500 ml) (40,48). After 24 hr, the solids were removed by filtration through Celite, and the filtrate was concentrated *in vacuo* to an oil which was crystallized from isopropyl ether at -3°C. Recrystallization from isopropyl ether gave 15 g of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside: m.p. 57-58.5°C, $[\alpha]_D^{29}$ -20.5 (*c* 1.2, $CHCl_3$).

Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (15 g) was dissolved in methanol (200 ml). Sodium methoxide (1N, 4 ml) in methanol was added and after 24 hr, the solution was neutralized with Amberlite IR 120 (H^+) resin. The methanolic solution was concentrated in vacuo to an oil (58% yield from the diacetate), which was then distilled through a 7-inch Vigreux column (b.p. 147-148°C; 0.20-mm Hg). The pure oil had $[\alpha]_D^{22}$ -29.8° (c 0.9, $CHCl_3$) (found: C, 58.9; H, 9.1. $C_{15}H_{28}O_6$ requires C, 59.2; H, 9.3%). The purified oil crystallized after storage for 6 months: m.p. 48.5-50°C; NMR $\delta(CDCl_3)$ 4.30 (1H, d, H-1, $J_{1,2}$ 6.5 H_2), 1.2-2.0 (10H, from cyclohexyl group), 3.40, 3.53, and 3.65 (3 × MeO), and 3.04 ppm (1H, s, OH-2).

ETHANOLYSES

SOLUTION PREPARATION

The procedure is a modification of Hultman's procedure (1). All glassware used in solution preparation was dried in an oven (110°C), followed by storage in a desiccator (potassium hydroxide).

Sufficient 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose to prepare a 0.068M solution was weighed into a volumetric flask. The volumetric flask and contents, anhydrous ethanol, anhydrous ethanolic solution of catalyst, and an anhydrous ethanolic solution of lithium p-toluenesulfonate (if needed) were thermostated at 25.0°C in a water bath for 30 minutes. Thermally equilibrated anhydrous ethanol was added to the volumetric flask containing the orthoester to about 60% of the final intended volume. The orthoester was dissolved with the aid of swirling. If necessary, the lithium p-toluenesulfonate solution was added at this point to make a 0.063N solution upon final dilution. The catalyst solution was added to make a 0.0052N

solution upon final dilution. The solution was then quickly diluted to volume, mixed thoroughly, and stored at 25.0°C. Time zero was taken to be the point at which one-half of the intended catalyst solution was added.

Contamination by water during sampling was minimized by utilization of the apparatus shown in Fig. 24 (1). To remove a sample for analysis, a pipet (1 ml) was placed in the rubber tube of the drying chamber and dry nitrogen was passed through the chamber. The clamp was opened and the pipet was pushed into the solution to withdraw an aliquot. The pipet was removed and the clamp closed until the next sample was taken.

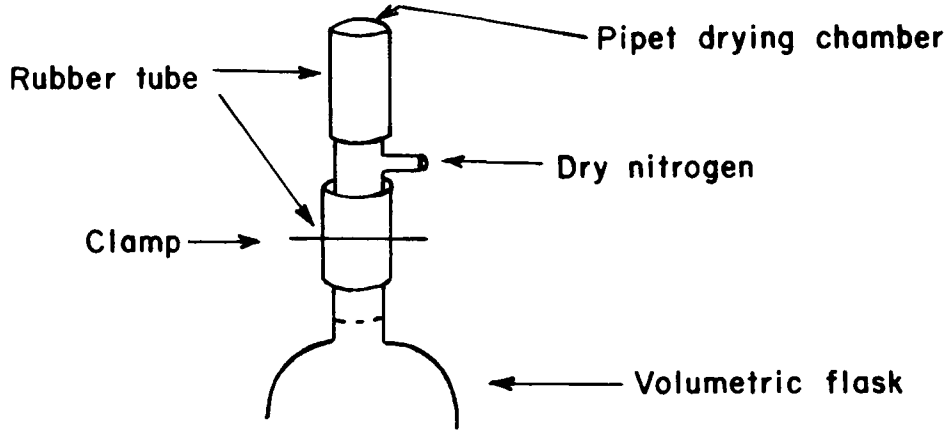


Figure 24. Sampling Apparatus Used to Minimize Contamination by Water (1)

KINETIC TECHNIQUES AND ANALYSES

Nuclear Magnetic Resonance Spectrometry

Exo-endo isomerization of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (0.0712M) in ethanolic 2,6-dichlorobenzoic acid (100 ml, 0.00528N) at 25.0°C was analyzed by the following procedure. At various times (37, 170, 411, and 684 min), a sample of the reaction (ca. 25 ml) was

added to 50 ml of triethylamine-toluene (3:7, v/v) to quench the reaction. The solution was concentrated *in vacuo* to *ca.* 2 ml. Benzene (4 ml) and a trace of pyridine was added, and the resulting solution was concentrated *in vacuo* to an oil. The samples were stored in a desiccator (potassium hydroxide) until NMR spectra ($CDCl_3$) could be obtained. The integrals of the methyl singlets of *exo*-ethoxy ($\delta \approx 1.72$ ppm) and *endo*-ethoxy ($\delta \approx 1.53$ ppm) isomers were used to determine the isomeric ratio. The results are given in Table I, and two of the spectra are reproduced in Fig. 4.

Polarimetry

The constant-temperature polarimetry system was of the same design as that used by Schroeder (37). The polarimeter cell used was glass with a glass jacket forming the annulus for circulating water around the tube. The tube was 1-dm long and held 5-6 ml of solution.

A sample of ethanolysis solution was added to the 1-dm water-jacketed standard polarimeter cell at 25.0°C. Readings were begun about two minutes from time zero. The polarimetric data collected are given in Appendix I.

The anomeric configuration of 3,4,6-tri-*O*-methyl-D-mannopyranose formed initially in the ethanolysis of 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose was determined using the following procedure. After 5.7 minutes of reaction, the picric acid-catalyzed ethanolysis solution (8 ml) was treated with a 15-fold excess of triethylamine (0.1 ml). The resulting solution was quickly transferred to a polarimetric cell, and the readings were taken as a function of time. The addition of triethylamine stopped the ethanolysis reaction (confirmed by GLC analysis) and simultaneously effected mutarotation of the reducing sugar in the system.

Carbohydrate Analysis

Product Identification

The reactant and carbohydrate products of the ethanolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose were identified by retention times and measured quantitatively by GLC. Prior to GLC analysis, ethanolysis samples were chemically modified to change the unreacted orthoester and carbohydrate products to derivatives which were stable under GLC conditions. The chemical modification involved: hydrolysis of unreacted 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose, and subsequent O-propanoylation of free hydroxyl groups of the carbohydrates.

Chromatogram A (Fig. 25) illustrates the GLC analysis of a synthetic mixture of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose and its expected ethanolysis products subjected to the procedure. The identities of the peaks are as follows:

1. Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside
2. Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside
3. Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (as the 2-O-propanoyl derivative)
4. Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (as the 2-O-propanoyl derivative)
5. 1-O-Acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose[8] [as O-propanoyl derivatives; these compounds are the hydrolysis products of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose]

[8] Swanson (49) demonstrated that mild acid-catalyzed hydrolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose yield 95-100% of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose. Thus, Peak 5, which corresponds to the hydrolysis products of the mannose 1,2-(ethyl orthoacetate) can be attributed to the mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses.

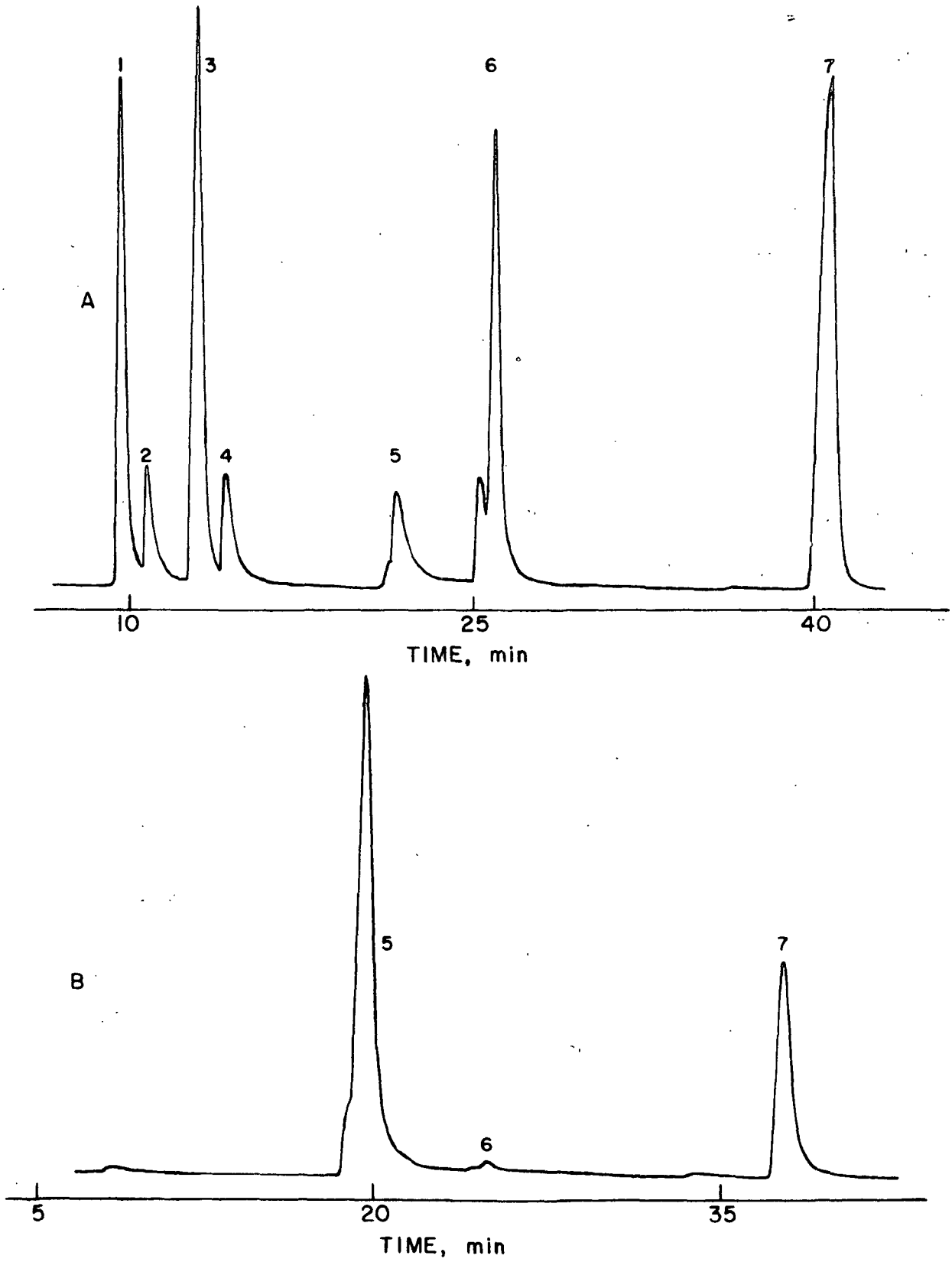


Figure 25. Sample Chromatograms. A, Known Mixture for Response Factor Determination; B, 2,6-Dichlorobenzoic Acid-Catalyzed Ethanolysis at 9.2 Min

6. 3,4,6-Tri-O-methyl-D-mannopyranose (as the 1,2-di-O-propanoyl derivatives, anomers partially separated)

7. Cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (as the 2-O-propanoyl derivative; this compound is the internal standard added for quantitative analysis)

Very little ethanolysis products appear in chromatogram B (Fig. 25) because the sample was taken shortly after initiation of the reaction. Since the ethanolysis sample was subjected to the hydrolysis-propanoylation work-up procedure, chromatogram B (Fig. 25) illustrates that the conversion of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose to 2-O-acetyl- and 1-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose by the acid-catalyzed hydrolysis step was essentially quantitative. As discussed previously (see Results), acid-catalyzed hydrolysis of the orthoester also produced a small amount of 3,4,6-tri-O-methyl-D-mannopyranose (ca. 3 mole%).

Chromatogram C (Fig. 26) illustrates an analysis of an ethanolysis (0.00512N picric acid, 652.5 min) after the reactant has been consumed. The small amount of 2-O-acetyl- and 1-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose (5) indicated that the orthoester underwent ethanolysis almost to completion and that no significant hydrolysis of the reactant occurred during ethanolysis.

Chromatogram D (Fig. 26) illustrates an analysis of an ethanolysis catalyzed by 0.00535N 2,6-dichlorobenzoic acid in 0.063N lithium p-toluenesulfonate (7422 min). Note the detection of a small quantity of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside (2).

Quantitative Analysis

The work-up procedure is a modification of Hultman's procedure (1). An aliquot (1.0 ml) of the ethanolysis solution was pipeted into 1.0 ml of a

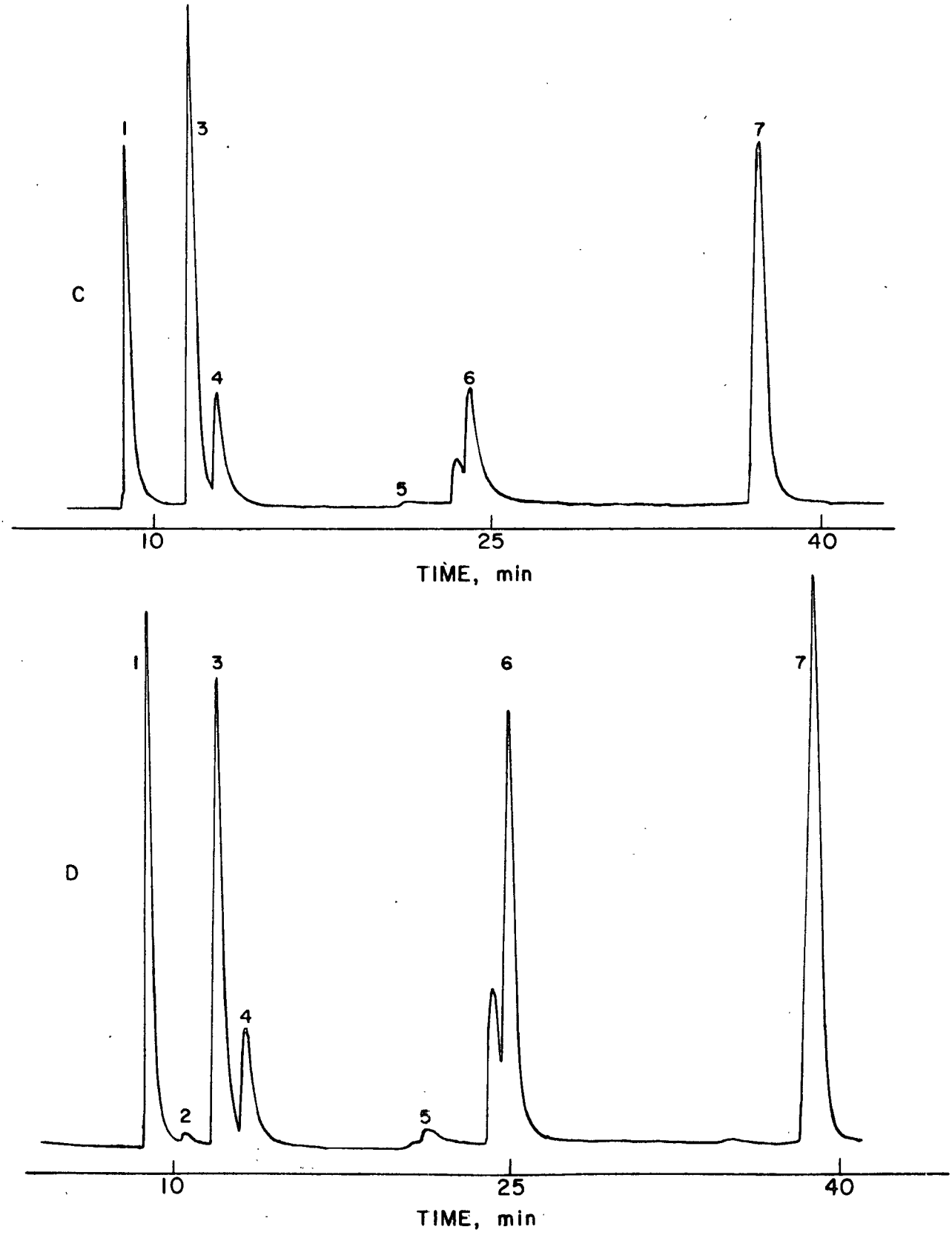


Figure 26. Sample Chromatograms. C, Picric Acid-Catalyzed Ethanolysis at 622.5 Min; D, Ethanolysis Catalyzed by 2,6-Dichlorobenzoic Acid in Lithium p-Toluenesulfonate at 7422 Min

standard solution of cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (0.017M) in triethylamine-toluene (3:7, v/v). A portion of the resultant solution (1 ml) was concentrated in vacuo (45°C bath) to an oil. An aqueous solution (4 ml) of brom cresol purple[9] was added to the oil. Sulfuric acid (1.0N, one drop) was added to the solution, and after 10 minutes, sodium hydroxide (0.01N) was added dropwise with swirling until the solution turned purple (pH ca. 5-7). Buffer (0.4 ml, 0.1M K_2HPO_4 and 0.1M KH_2PO_4) was added, and the solution was concentrated in vacuo to ca. 0.5 ml. Drying of the sample was completed by storing the open flask in a desiccator (potassium hydroxide) under vacuum for a minimum of 5 hr.

The dried sample was treated with pyridine-propanoic anhydride (ca. 1.5 ml; 5:3, v/v) and mechanically shaken for 72 hr. Water (10 ml) was added and after 15 minutes, the solution was extracted with chloroform (3 × 15 ml). The extracts were washed with 2N hydrochloric acid in a saturated sodium chloride solution (5 ml), a saturated solution of sodium bicarbonate in 10% sodium chloride (8 ml), and water (10 ml). After each of the above washings, the aqueous phase was back-extracted with a comparable volume of chloroform and the chloroform solutions were combined before the next step.

The resultant chloroform solution was concentrated in vacuo. Water was added to the sample, and the solution was reconcentrated to remove residual propanoic acid. The resultant oil was dried in a desiccator (potassium hydroxide) for several hr, dissolved in acetone (1-2 ml), and analyzed by GLC (triplicate analyses, Conditions A).

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[9] Brom cresol purple indicator (Harleco, 0.04% solution) (2.5 ml) was added to distilled water (200 ml).

The response factors required for quantitative GLC were determined by treatment of synthetic mixtures of the necessary components in ethanol by the above procedure. The values are given in Appendix IV.

Ethyl Acetate Analysis

Product Identification

GLC (Conditions B) provided a means of identifying ethyl acetate (by retention time) formed in ethanolysis. However, previous work (1) indicated that triethyl orthoacetate was partially hydrolyzed to ethyl acetate during GLC analysis. Therefore, accurate quantitative estimates of ethyl acetate formed in ethanolysis could not be obtained. For this reason, ethanolysis samples were treated with aqueous acid to hydrolyze triethyl orthoacetate to ethyl acetate and ethanol before GLC analysis. The ethyl acetate analysis, therefore, represented the mole fraction of ethyl acetate plus triethyl orthoacetate formed in ethanolysis.

A sample chromatogram is shown in Fig. 27. The identities of the peaks are: ethyl acetate (1) and n-butyl acetate (2, the internal standard).

Quantitative Analysis

An aliquot (1.0 ml) of the ethanolysis solution was pipeted into 1.0 ml of a standard solution of n-butyl acetate (0.019M) in dilute sulfuric acid (0.018N)[10]. The sample was neutralized with Amberlite MB-3 ion-exchange resin, decanted, and analyzed by GLC (triplicate analyses, Conditions B) as soon as possible.

[10] The solution was prepared just prior to use to minimize acid-catalyzed hydrolysis of n-butyl acetate.

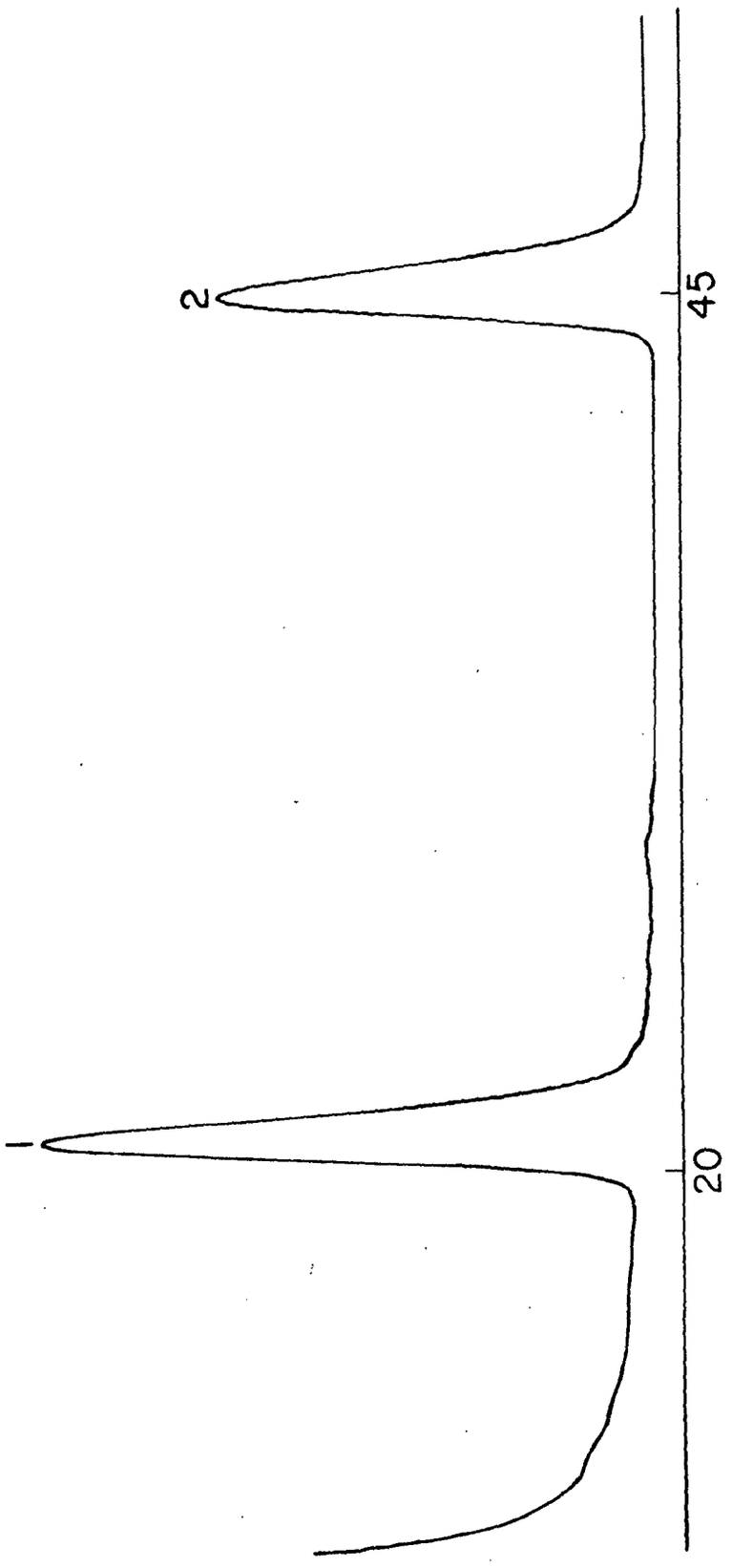


Figure 27. Sample Chromatogram for Ethyl Acetate Analysis

The response factors required for quantitative GLC were determined by treatment of synthetic solutions (in ethanol) of ethyl acetate and of triethyl orthoacetate by the above procedure. The values are given in Appendix IV.

REACTIONS WITH ETHANOL IN VARIOUS SOLVENTS

An aliquot (2.0 ml) of a stock picric acid solution was added to a 25-ml volumetric flask (to give 0.0047N acid on final dilution). If necessary, additional anhydrous ethanol was added at this point to give the desired alcohol concentration on final dilution. The ethanolic solution was then diluted to 25.0 ml with the desired solvent (dichloromethane or nitromethane).

1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (0.10 g) was weighed into an NMR tube and the desired solution (0.50 ml) was added. The reaction was followed by NMR in the range $1.2 < \delta < 2.5$ ppm. The peaks of interest were $\delta \approx 2.09$ (acetylated mannopyranosides), $\delta \approx 2.00$ (ethyl acetate), $\delta \approx 1.63$ (exo-ethoxy isomer), $\delta \approx 1.48$ (endo-ethoxy isomer), and $\delta \approx 1.41$ ppm (triethyl orthoacetate). The reaction solution was added to toluene-triethylamine (5 ml; 7:3, v/v) to quench the reaction when the exo- and endo-ethoxy orthoester singlets were less than 10% of their original height. The solution was concentrated *in vacuo* and worked up for GLC analysis (Conditions A) as previously described for ethanolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose. Analyses are given in Table VI. A series of NMR scans for one of the reactions is reproduced in Fig. 7.

REACTIONS IN AQUEOUS ETHANOL

Standard ethanol-water solutions were made up by weighing water into a volumetric flask, adding an aliquot of standard ethanolic solution of picric

acid (to give 0.005N acid on final dilution), diluting to volume with anhydrous ethanol, and reweighing. 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (ca. 0.2 g) was then weighed into a 10-ml volumetric flask. The volumetric flask with contents and the standard ethanol-water solution were thermostated at 25.0°C for 20 minutes. The ethanol-water solution was then used to dilute the orthoester to 10.0 ml. In calculations, it was assumed that the density of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose is 1-g ml^{-1} and that the volumes are additive.

The identification and subsequent quantitative analyses of the carbohydrate products were made by GLC (Conditions A). The samples were treated as previously described for ethanolyses of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose.

ETHANOLYSES OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

3,4,6-Tri-O-methyl-α-D-mannopyranose (1.338 g) was weighed into a volumetric flask (100 ml), diluted with anhydrous ethanol (ca. 50 ml), and stored at 25.0°C overnight. Triethyl orthoacetate (1.821 g) in a volumetric flask, anhydrous ethanol, and a solution of picric acid (ca. 15 ml) sufficient to give a 0.0053N solution on final dilution were thermostated at 25.0°C for 60 minutes. Anhydrous ethanol (ca. 25 ml) was added to the orthoester, and the resultant solution was added to the 3,4,6-tri-O-methyl-D-mannopyranose solution. The picric acid solution was added at time zero. The solution was quickly diluted to 100.0 ml with ethanol, and the sampling apparatus (see Fig. 24) was then attached.

The identification by retention time and subsequent quantitative analyses of the carbohydrates were made by GLC (Conditions A). The samples were worked up as previously described for ethanolyses of 1,2-*O*-[1-(*exo*-ethoxy)-ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose.

ACID-CATALYZED HYDROLYSES OF ETHYL 2-*O*-(1,1-DIETHOXYETHYL)-3,4,6-TRI-*O*-METHYL-α-D-MANNOPYRANOSIDE IN VARIOUS SOLVENTS

Picric acid (0.029 g) and water (0.40 g) were weighed into each of four 25-ml volumetric flasks. The aqueous acid suspension was diluted to 25.0 ml with the desired solvent (ethyl ether, ethanol, nitromethane, or water), and thermostated at 25.0°C for 1 hr. Impure ethyl 2-*O*-(1,1-diethoxyethyl)-3,4,6-tri-*O*-methyl-α-D-mannopyranoside (0.12 g) was weighed into each of four 5-ml volumetric flasks. The desired reaction solution was added to the 5-ml mark of each flask, and the reaction solutions were stored at 25.0°C for 3 hr.

The reaction solutions were added to equal volumes of triethylamine-toluene (3:7, v/v). A portion (1 ml) of each of the four solutions were concentrated *in vacuo*, dried in a desiccator (potassium hydroxide) under vacuum for several hr, propanolyated with pyridine-propanoic anhydride (*ca.* 1.5 ml; 5:3, v/v) for 72 hr, and treated as previously described for ethanolyses of 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose.

NOMENCLATURE

f_X = GLC response factor for component X

k_i = specific first-order rate constant for the formation of product i

k_j = specific second-order rate constant for the formation of product j

k_r = specific first-order rate constant for the disappearance of the glycose 1,2-(ethyl orthoacetate)

k_{rs} = specific second-order rate constant for the disappearance of 3,4,6-tri-O-methyl-D-mannopyranose and triethyl orthoacetate

ortho = 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose

TMM = 3,4,6-tri-O-methyl-D-mannopyranose

TRI = triethyl orthoacetate

$X_{exo}(t)$ = mole fraction of exo-ethoxy isomer at time t

$X_{i,t}$ = mole fraction of component i at time t

$X_{i,\infty}$ = the relative proportion of product i formed

$X_{r,t}$ = mole fraction of reactant at time t

α = observed optical rotation, °

$\alpha_m(t)$ = molar specific rotation defined by Equation (1)

$[\alpha]_{\lambda}^{t^\circ}$ = the specific rotation of a substance at temperature t, using plane polarized radiation of wavelength λ

α Et = ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside

α Et 2-O-Ac = ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside

β Et = ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside

β Et 2-O-Ac = ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside

Products and intermediates:

I = 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose

II = ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside

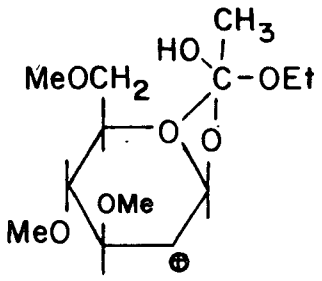
III = ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside

IV = ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside

V = ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside

VI = 3,4,6-tri-O-methyl-D-mannopyranose

VII =



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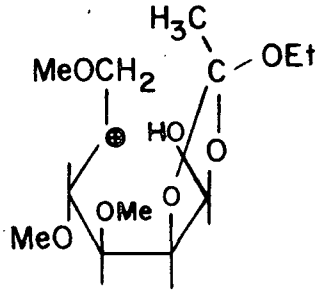

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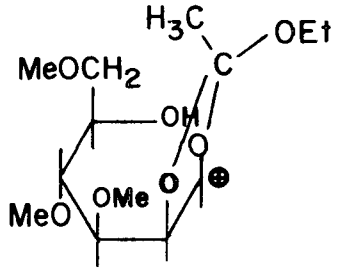

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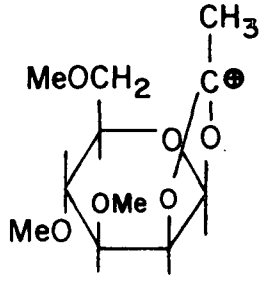

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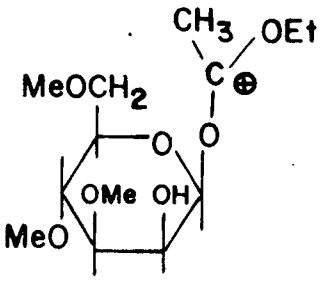
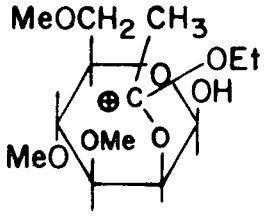


XII =



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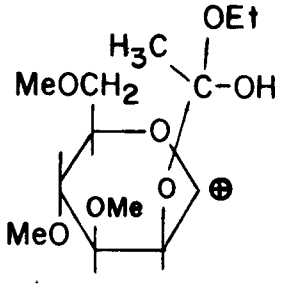


XIV = 2-O-(1-ethoxy-1-hydroxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose

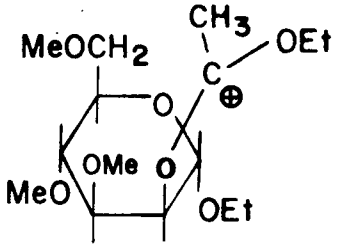
XV = 1-O-(1-ethoxy-1-hydroxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose

XVI = 1,2-O-(1-hydroxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose

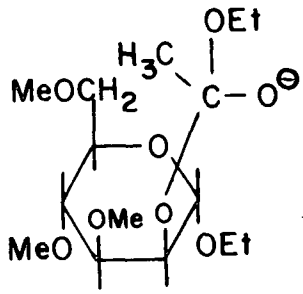
XVII = 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannopyranose

XVIII = 1,1-diethoxyethyl cation

XIX =



XX = ethyl 2-O-(1-ethoxy-1-hydroxyethyl)-3,4,6-tri-O-methyl-α-D-manno-pyranoside

XXI = 

XXII = 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-β-D-mannpyranose

XXIII = 3,4,6-tri-O-methyl-D-mannopyranosyl cation

XXIV = 2-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranose

XXV = 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-α-D-mannopyranose

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APPENDIX I

POLARIMETRIC DATA

Tables X-XII contain polarimetric data for three ethanolyses. Table XIII contains polarimetric data for the mutarotation of 3,4,6-tri-O-methyl-α-D-mannopyranose at 25.0°C in ethanolic 0.00526N picric acid. Table XIV contains the polarimetric constants necessary to simulate the polarimetric data for the ethanolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose.

TABLE X

ETHANOLYSIS OF 1,2-O-[1(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00526N 2,6-DICHLOROBENZOIC ACID

Time, min	α, °[b]	Time, min	α, °[b]
2.3	0.170	140.0	0.074
3.0	0.169	152.0	0.070
4.0	0.169	160.0	0.067
5.0	0.168	177.0	0.061
8.5	0.165	190.0	0.058
10.0	0.163	202.0	0.055
12.5	0.159	214.0	0.051
15.0	0.156	222.0	0.049
17.5	0.154	230.0	0.047
20.0	0.152	240.0	0.046
25.0	0.147	252.0	0.045
33.5	0.139	268.0	0.042
35.0	0.138	275.0	0.041
40.0	0.134	290.0	0.040
47.5	0.127	300.0	0.039
60.0	0.118	338.0	0.037
72.0	0.110	358.0	0.038
81.0	0.105	396.0	0.040
94.0	0.097	442.0	0.042
103.0	0.092	476.0	0.044
109.0	0.089	507.0	0.048
126.0	0.080	614.0	0.064
130.0	0.079	880.0	0.110

[a] 0.0690M.

[b] 1-dm Cell, 546-nm light.

TABLE XI

ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00527N PICRIC ACID[b]

Time, min	α, °C[c]	Time, min	α, °C[c]
2.3	0.120	24.8	0.797
2.5	0.135	25.5	0.805
5.5	0.310	26.0	0.809
7.7	0.405	27.0	0.818
9.8	0.480	28.0	0.825
12.0	0.555	29.0	0.833
15.0	0.638	30.0	0.841
15.5	0.649	31.0	0.849
16.0	0.660	33.0	0.860
16.5	0.671	49.8	0.922
17.0	0.681	134.0	1.000
18.0	0.700	193.5	1.021
19.0	0.717	258.5	1.033
20.5	0.742	324.8	1.042
21.0	0.749	360.5	1.044
22.0	0.763	483.0	1.048
22.5	0.770		

[a] 0.0686M.

[b] GLC data for this kinetic run are given in Table XII; ethyl acetate plus triethyl orthoacetate data, in Table IV.

[c] 1-dm Cell, 546-nm light.

TABLE XII

MUTAROTATION OF THE 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE FORMED IN THE ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00532N PICRIC ACID

Time,[b] min	α, °[c,d]	α, °[c,e]	Time,[b] min	α, °[c,d]	α, °[c,e]
1.3	0.029	--	12.0	--	0.272
2.0	0.035	--	13.0	--	0.274
2.5	0.055	--	14.0	--	0.278
3.0	0.079	--	15.0	0.578	--
3.5	0.106	--	16.0	0.602	--
4.0	0.134	--	17.0	0.622	--
4.5	0.162	--	18.0	0.643	--
5.0	0.190	--	19.0	0.662	--
5.5	0.218	--	20.0	0.680	--
5.7	--	(quench)	21.0	--	0.284
6.0	0.244	--	25.0	--	0.286
6.5	0.270	--	30.5	0.799	--
7.0	--	0.230	38.0	0.843	--
7.5	--	0.236	43.0	0.868	--
8.0	--	0.242	52.0	0.890	--
8.5	--	0.249	57.0	0.901	--
9.0	--	0.253	60.0	--	0.286
10.0	0.422	--	88.0	0.939	--
10.5	0.422	--	143.0	0.972	--
11.5	--	0.270	146.0	--	0.283

[a] 0.0672M.

[b] Time from starting ethanolysis.

[c] 1-dm Cell, 546-nm light.

[d] Ethanolysis with no triethylamine addition.

[e] Ethanolysis with triethylamine addition at 5.7 min. GLC analysis indicated that there was no further reaction of the orthoester after the triethylamine was added.

TABLE XIII

MUTAROTATION OF 3,4,6-TRI-O-METHYL-α-D-MANNOPYRANOSE[a] AT 25.0°C IN ETHANOLIC 0.00526N PICRIC ACID

Time, sec	α, °[b]
65	1.078
70	1.066
80	1.067
90	1.065
100	1.061
110	1.060
120	1.057
130	1.054
140	1.051
150	1.049
170	1.044
180	1.042
210	1.037
240	1.033
300	1.031
360	1.024
390	1.023
∞	1.023

[a] 0.1105M.

[b] 1-dm Cell, 546-nm light.

The mutarotation constant of 3,4,6-tri-O-methyl-α-D-mannopyranose can be calculated from the data in Table XIII to be $k_{\alpha\rightarrow\beta} + k_{\beta\rightarrow\alpha} = 0.0094$ sec^{-1} where mutarotation is considered to be a simple first-order, reversible reaction of the form:

$$\alpha\text{-anomer} \underset{k_{\beta\rightarrow\alpha}}{\overset{k_{\alpha\rightarrow\beta}}{\rightleftarrows}} \beta\text{-anomer}$$

TABLE XIV

POLARIMETRIC CONSTANTS IN ETHANOL

Compound	$[\alpha]^{28}_{546\ nm}$, (°)
Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside	70.2
Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside	-80.9
Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside	95.8
Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside	-74.7
3,4,6-Tri-O-methyl-α-D-mannopyranose	46.8 → 41.2
1,2-O-[1-Ethoxyethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose	
exo-ethoxy isomer (pure)	8.4
exo-ethoxy-endo-ethoxy equilibrium mixture[a]	-4.9

[a] Extrapolated from polarimetric data (Tables XI and XII) when plotted as log $[\alpha_\infty - \alpha_t]$ vs. time where $\alpha_\infty = 0.86$.

APPENDIX II

RATE OF EXO-ENDO ISOMERIZATION

The following two assumptions were made in order to determine the rate of exo-endo isomerization of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose in 25.0°C ethanolic 0.00528N 2,6-dichlorobenzoic acid:

1. The rate of isomerization is fast relative to the rate of mannose orthoester disappearance. (The results indicate that isomerization was ca. 9 times faster than orthoester disappearance.)
2. Exo-endo isomerization may be represented by the equation for a first-order, reversible reaction.

These two assumptions lead to the following equations:

$$\frac{d[X_{exo}(t)]}{dt} = -k_{exo\rightarrow endo}[X_{exo}(t)] + k_{endo\rightarrow exo}[X_{endo}(t)], \qquad (15)$$

$$[X_{exo}(t)] = 1 - [X_{endo}(t)]. \qquad (16)$$

Initial condition:

$$X_{endo}(0) = 0.0, \qquad (17)$$

where $X_{exo}(t)$ = mole fraction of exo-ethoxy isomer in terms of total mannose orthoester

$X_{endo}(t)$ = mole fraction of endo-ethoxy isomer in terms of total mannose orthoester

$k_{exo\rightarrow endo}$ = specific first-order rate constant for the formation of the endo-ethoxy isomer

$k_{endo\rightarrow exo}$ = specific first-order rate constant for the formation of the exo-ethoxy isomer

Substituting for $[\underline{X}_{exo}(\underline{t})]$ [from Equation (16)] into Equation (15) one obtains:

$$\frac{d[X_{endo}(t)]}{dt} = k_{exo\rightarrow endo}\{1 - [X_{endo}(t)]\} - k_{endo\rightarrow exo}[X_{endo}(t)]. \quad (18)$$

Solving Equations (17)-(18) by separation of variables, one obtains Equation (19):

$$X_{endo}(t) = \left(\frac{k_{exo\rightarrow endo}}{k_{exo\rightarrow endo} + k_{endo\rightarrow exo}}\right)\{1 - \exp[-(k_{exo\rightarrow endo} + k_{endo\rightarrow exo})t]\}. \quad (19)$$

At equilibrium,

$$\left(\frac{X_{endo}}{X_{exo}}\right)_{eq.} = \frac{k_{exo\rightarrow endo}}{k_{endo\rightarrow exo}} = 0.37 \quad (20)$$

as shown in Table I.

Substituting for $k_{exo\rightarrow endo}$, Equation (19) reduces to the following:

$$X_{endo}(t) = 0.27\,[1 - \exp(-1.37\,k_{endo\rightarrow exo}t)]. \quad (21)$$

From the data given in Table I, the rate constants $k_{exo\rightarrow endo}$ and $k_{endo\rightarrow exo}$ can be calculated. The values found were $k_{exo\rightarrow endo} = 0.40 \times 10^{-4}$ sec^{-1} and $k_{endo\rightarrow exo} = 1.1 \times 10^{-4}$ sec^{-1}.

APPENDIX III

QUANTITATIVE GLC DATA FOR ETHANOLYSES

This appendix contains reactant and product distribution data as a function of time for acid-catalyzed ethanolyses of 1,2-O-[1-(exo-ethoxy)-ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (Tables XV-XVII). Also see Table II of the Results section.

TABLE XV

ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00527N PICRIC ACID[b]

Time, min	Mole Fraction[c,d]				
	Products				Reactant
	α Et 2-O-Ac[e]	α Et[f]	β Et[g]	TMM[h]	Orthoester
9.8	0.115 (2)	0.100 (4)	0.005 (1)	0.377 (4)	0.403 (2)
19.8	0.161 (9)	0.153 (7)	0.009 (1)	0.467(11)	0.210(12)
31.6	0.204 (5)	0.202 (7)	0.023 (4)	0.458(10)	0.113 (5)
138.0	0.235(10)	0.346 (6)	0.074 (5)	0.318(17)	0.027 (6)

[a] 0.0686M.

[b] Polarimetric data on this run may be found in Table XI; ethyl acetate data, in Table IV.

[c] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[d] Normalized data.

[e] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[f] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[g] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[h] 3,4,6-Tri-O-methyl-D-mannopyranose.

TABLE XVI

ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.00528N 2,6-DICHLOROBENZOIC ACID

Time, min	Mole Fraction[b]					
	Products				Reactant Orthoester	Total Measured
	α Et 2-O-Ac[c]	α Et[d]	β Et[e]	TMM[f]		
9.2	0.000 (0)	0.000 (0)	0.000 (0)	0.000 (0)	0.956(30)	0.956(30)
170.0	0.010 (5)	0.003 (3)	0.000 (0)	0.078 (5)	0.862(22)	0.953(20)
365.0	0.030 (8)	0.025(10)	0.000 (0)	0.111 (7)	0.830(16)	0.997(19)
660.0	0.046 (7)	0.034 (6)	0.000 (0)	0.172 (9)	0.722(28)	0.974(35)
1323.0	0.065 (9)	0.055 (8)	0.000 (0)	0.250(20)	0.570(14)	0.941(46)
2035.0	0.085 (9)	0.077 (8)	0.000 (0)	0.333(12)	0.489 (6)	0.984(35)
2808.0	0.101 (7)	0.090 (3)	0.002 (1)	0.382 (5)	0.397 (6)	0.972 (8)
3610.0	0.116 (9)	0.112 (3)	0.007 (3)	0.437(12)	0.338(14)	1.010(17)
4517.0	0.125(12)	0.115 (6)	0.009 (4)	0.449 (4)	0.278 (3)	0.976(31)
5738.0	0.141(11)	0.136 (2)	0.009 (1)	0.497(12)	0.229 (4)	1.012(21)
7350.0	0.127 (9)	0.141 (8)	0.009 (2)	0.499 (8)	0.176(14)	0.953(22)
8666.0	0.153(10)	0.168 (8)	0.016 (4)	0.505 (6)	0.150(11)	0.992(33)
10193.0	0.155 (3)	0.175(10)	0.019 (5)	0.531(15)	0.128 (9)	1.007(28)
13035.0	0.151(10)	0.176(10)	0.024 (1)	0.511 (8)	0.095 (4)	0.957(23)

[a] 0.0684M.

[b] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[f] 3,4,6-Tri-O-methyl-D-mannopyranoside.

TABLE XVII

ETHANOLYSIS OF 1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-3,4,6-TRI-O-METHYL-β-D-MANNOPYRANOSE[a] AT 25.0°C IN 0.063N LITHIUM p-TOLUENESULFONATE AND 0.00535N 2,6-DICHLOROBENZOIC ACID

Time, min	Mole Fraction[b]						
	Products					Reactant Orthoester	Total Measured
	α Et 2-O-Ac[c]	β Et 2-O-Ac[d]	α Et[e]	β Et[f]	TMM[g]		
2.3	0.000 (0)	0.000 (0)	0.000 (0)	0.000 (0)	0.000 (0)	1.004(13)	1.004(13)
39.0	0.016(10)	0.000 (0)	0.007 (0)	0.000 (0)	0.035 (5)	0.892(27)	0.951(39)
129.5	0.056 (7)	0.000 (0)	0.035 (1)	0.001 (1)	0.123 (6)	0.776(19)	0.990(29)
265.0	0.085 (2)	0.000 (1)	0.061 (4)	0.011 (2)	0.198 (4)	0.625(10)	0.980(16)
403.5	0.115 (6)	0.002 (1)	0.080 (3)	0.016 (3)	0.238 (9)	0.515 (7)	0.966(18)
664.1	0.165 (5)	0.006 (2)	0.126 (5)	0.025 (4)	0.341 (9)	0.366 (9)	1.027(33)
1148.1	0.195 (2)	0.007 (1)	0.158 (6)	0.034 (4)	0.390 (3)	0.233 (8)	1.016(20)
1731.5	0.216 (6)	0.007 (1)	0.188 (9)	0.042 (2)	0.403(11)	0.149 (5)	1.005(25)
3032.0	0.229(14)	0.008 (2)	0.202 (7)	0.052 (4)	0.376 (3)	0.072 (8)	0.939(11)
7422.0	0.242 (3)	0.009 (3)	0.264 (5)	0.076 (3)	0.343(11)	0.026 (5)	0.959(11)

[a] 0.0686M.

[b] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[c] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[d] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside.

[e] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[f] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[g] 3,4,6-Tri-O-methyl-D-mannopyranose.

APPENDIX IV

GLC RETENTION TIMES AND RESPONSE FACTORS

The retention times and response factors for the reactant and carbohydrate products of acid-catalyzed ethanolyses of 1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-3,4,6-tri-*O*-methyl-β-D-mannopyranose are presented in Table XVIII. The retention time and response factor for ethyl acetate are given in Table XIX. The retention times listed varied slightly with the age and loading of the column.

The response factors required for quantitative analysis of ethanolyses were obtained from synthetic mixtures of the reactant and products in ethanol.

The mole fraction of each component identified and measured by GLC is given by Equation (22):

$$X_{r,t} \text{ or } X_{i,t} = \frac{1}{f_x}\left(\frac{\text{area X}}{\text{area standard}}\right)\left(\frac{\text{moles standard}}{\text{moles reactant}}\right), \qquad (22)$$

where $X_{r,t}$ = mole fraction of reactant remaining at time t in terms of original reactant

$X_{i,t}$ = mole fraction of product i at time t in terms of original reactant

area X = peak area of component X at time t

area standard = peak area of internal standard on the same chromatogram

moles standard = moles of internal standard in the sample

moles reactant = moles of reactant, equated at time zero, in the sample

TABLE XVIII

RETENTION TIMES AND RESPONSE FACTORS[a] OF ETHANOLYSIS REACTANT AND CARBOHYDRATE PRODUCTS[b]

	Retention Time, min	Response Factor ($f_{\underline{X}}$)[c]
1,2-O-[1-Ethoxyethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose (as O-propanoyl derivative of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranose)	20.5	0.655
Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside	9.0	0.648
Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-mannopyranoside	10.4	0.655
Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (as the 2-O-propanoyl derivative)	12.0	0.685
Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (as the 2-O-propanoyl derivative)	13.4	0.709
3,4,6-Tri-O-methyl-D-mannopyranose (as the 1,2-di-O-propanoyl derivative)	24.4	0.708

[a] Response factors are relative to cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (as the 2-O-propanoyl derivative) which has a retention time of 38.0 min.

[b] GLC Conditions A (see Experimental) were employed.

[c] $f_{\underline{X}}$ = (Area X/area standard)(moles standard/moles X).

TABLE XIX

RETENTION TIME AND RESPONSE FACTOR[a] OF ETHYL ACETATE[b]

	Retention Time, min	Response Factor ($f_{\underline{x}}$)[c]
Ethyl acetate	21.0	0.663
Triethyl orthoacetate (as the hydrolysis product, ethyl acetate)	21.0	0.657

[a] Response factors are relative to n-butyl acetate, which has a retention time of 47 min.

[b] GLC Conditions B (see Experimental) were employed.

[c] $f_{\underline{x}}$ = (Area X/area standard)(moles standard/moles X).

Acid-catalyzed hydrolysis of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose yields a small amount of 3,4,6-tri-O-methyl-D-mannopyranose (ca. 3 mole%). Since acid-catalyzed hydrolysis is part of the sample work-up procedure, the mole fraction of 3,4,6-tri-O-methyl-D-mannopyranose (TMM) formed in ethanolysis is given by Equation (23):

$$X_{TMM,t}\left[\begin{array}{l}\text{from ethanoly-}\\ \text{sis reaction}\end{array}\right] = X_{TMM,t}\ [\text{Eq. (22)}] - 0.03X_{r,t}\ [\text{Eq. (22)}]. \qquad (23)$$

The response factor ($f_{\underline{x}}$) used for mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses (see Table VII) was not obtained directly. The only reasonable products from the acid-catalyzed hydrolysis of 1,2-O-[1-(exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose are 3,4,6-tri-O-methyl-D-mannopyranose, and mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses (1). Swanson (49) found (by NMR analysis) that mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses accounted for 95-100% of the hydrolysis products of the mannose 1,2-(ethyl

orthoacetate). The present work indicates that 3,4,6-tri-O-methyl-D-mannopyranose accounts for 3 mole% of the hydrolysis products leaving mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses to account for 97 mole%. Since the response factor (f_x) of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose was based solely on the peak for mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses (which accounted for 97 mole% of the hydrolysis products), the response factor (f_x) for mono-O-acetyl-3,4,6-tri-O-methyl-D-mannopyranoses was estimated to be $f_{\text{mannose 1,2-(ethyl orthoacetate)}}/0.97 = 0.675$.

APPENDIX V

QUANTITATIVE GLC DATA FOR ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

This appendix contains the reactant and product distribution data as a function of time for an acid-catalyzed ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate (Table XX). Also see Table V of the Results section.

TABLE XX

ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE[a] IN THE PRESENCE OF TRIETHYL ORTHOACETATE[b] IN 0.00531N PICRIC ACID AT 25.0°C

Time, min	Mole Fraction[c,d]				
	Products			Intermediate[e]	Reactant[e]
	α Et 2-O-Ac[f]	α Et[g]	β Et[h]	Orthoesters[i]	TMM[j]
3.1	0.000 (0)	0.041 (5)	0.013 (4)	0.048 (3)	0.899 (7)
21.0	0.013 (1)	0.169 (1)	0.069 (2)	0.104 (6)	0.645 (5)
36.3	0.033 (3)	0.242 (5)	0.098 (1)	0.106 (8)	0.520 (8)
63.6	0.064 (2)	0.340 (7)	0.130 (3)	0.070 (9)	0.396 (1)
112.1	0.091(15)	0.450(22)	0.162 (2)	0.031(19)	0.266 (5)
178.6	0.114 (1)	0.500 (9)	0.187 (6)	0.007 (7)	0.192 (3)
250.2	0.129 (9)	0.538(14)	0.202 (5)	0.001 (2)	0.129(11)
395.1	0.130 (2)	0.576(13)	0.220 (3)	0.000 (0)	0.074(11)
694.3	0.142 (4)	0.614(10)	0.225 (9)	0.000 (0)	0.019 (5)

[a] 0.0910M.

[b] 0.1121M.

[c] Figures in parentheses are the range for three analyses of the same sample multiplied by 10^3.

[d] Normalized data.

[e] Intermediate and reactant values are minimum and maximum values, respectively.

[f] Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside.

[g] Ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside.

[h] Ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside.

[i] 1,2-O-(1-Ethoxyethylidene)-, 2-O-(1,1-diethoxyethyl)-, and 1-O-(1,1-diethoxyethyl)-3,4,6-tri-O-methyl-D-mannopyranose are potential intermediates.

[j] 3,4,6-Tri-O-methyl-D-mannopyranose.

APPENDIX VI

A TEST TO DETERMINE THE RATE EQUATION FOR THE ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-D-MANNOPYRANOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

Experimentally it was found that ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside, ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside, and 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose were formed in parallel reactions (see Fig. 10). If the rate of the acid-catalyzed ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate is first-order in both the reducing sugar and the orthoester, the following rate equations will describe the reactions:

$$\frac{d[\text{ortho}]}{dt} = k_4[\text{TMM}][\text{TRI}], \tag{24}$$

$$\frac{d[\alpha\ \text{Et}]}{dt} = k_5[\text{TMM}][\text{TRI}], \tag{25}$$

$$\frac{d[\beta\ \text{Et}]}{dt} = k_6[\text{TMM}][\text{TRI}], \tag{26}$$

where ortho = 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose formed "directly" from the reaction of TMM with TRI [Equation (6) gives the mole fraction]

α Et = ethyl 3,4,6-tri-O-methyl-α-D-mannopyranoside formed "directly" from the reaction of TMM with TRI [Equation (7) gives the mole fraction]

β Et = ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside formed "directly" from the reaction of TMM with TRI

TMM = 3,4,6-tri-O-methyl-D-mannopyranose

TRI = triethyl orthoacetate

k_j = (j = 4,5,6) second-order rate constant for the formation of product j, liters/mole sec

t = sec

If one of the three equations [Equations (24)-(26)] is shown to be valid, the other two equations must also be valid since the products were formed in parallel reactions.

Rearranging, and integrating Equation (26) between the limits 0 and $\underline{t}$, one obtains Equation (27).

$$\int_o^t d[\beta\ Et] = \beta\ Et(t) = k_6 \int_o^t [TMM(t)][TRI(t)]dt. \qquad (27)$$

3,4,6-Tri-O-methyl-D-mannopyranose (TMM) and ethyl 3,4,6-tri-O-methyl-β-D-mannopyranoside (β Et) were measured by GLC. Triethyl orthoacetate (TRI) was not measured directly, but was determined by stoichiometry since one mole of triethyl orthoacetate reacts with one mole of 3,4,6-tri-O-methyl-D-mannopyranose. Thus, the molar concentration of triethyl orthoacetate is related to the 3,4,6-tri-O-methyl-D-mannopyranose concentration by Equation (28).

$$[TRI(t)] = [TRI(0)] + [TMM(t)] - [TMM(0)]. \qquad (28)$$

Substituting for [TRI($\underline{t}$)] [from Equation (28)], one obtains Equation (29).

$$[\beta\ Et(t)] = k_6 \int_o^t [TMM(t)]\ \{[TRI(0)] + [TMM(t)] - [TMM(0)]\}dt. \qquad (29)$$

The integral in Equation (29) was evaluated by the trapezoidal rule (50). The plot [β Et] vs. $\int_o^t [TMM(\underline{t})][TRI(\underline{t})]d\underline{t}$ was linear as shown in Fig. 28, thus proving that the acid-catalyzed ethanolysis of 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate is first-order in both the reducing sugar and the orthoester. The slope of the curve in Fig. 28 is equal to $\underline{k}_6$. Similar plots based on Equations (24) and (25) were also made for both kinetic runs studied. The average rate constants ($\underline{k}_4$, $\underline{k}_5$, and $\underline{k}_6$) found are reported in the text.

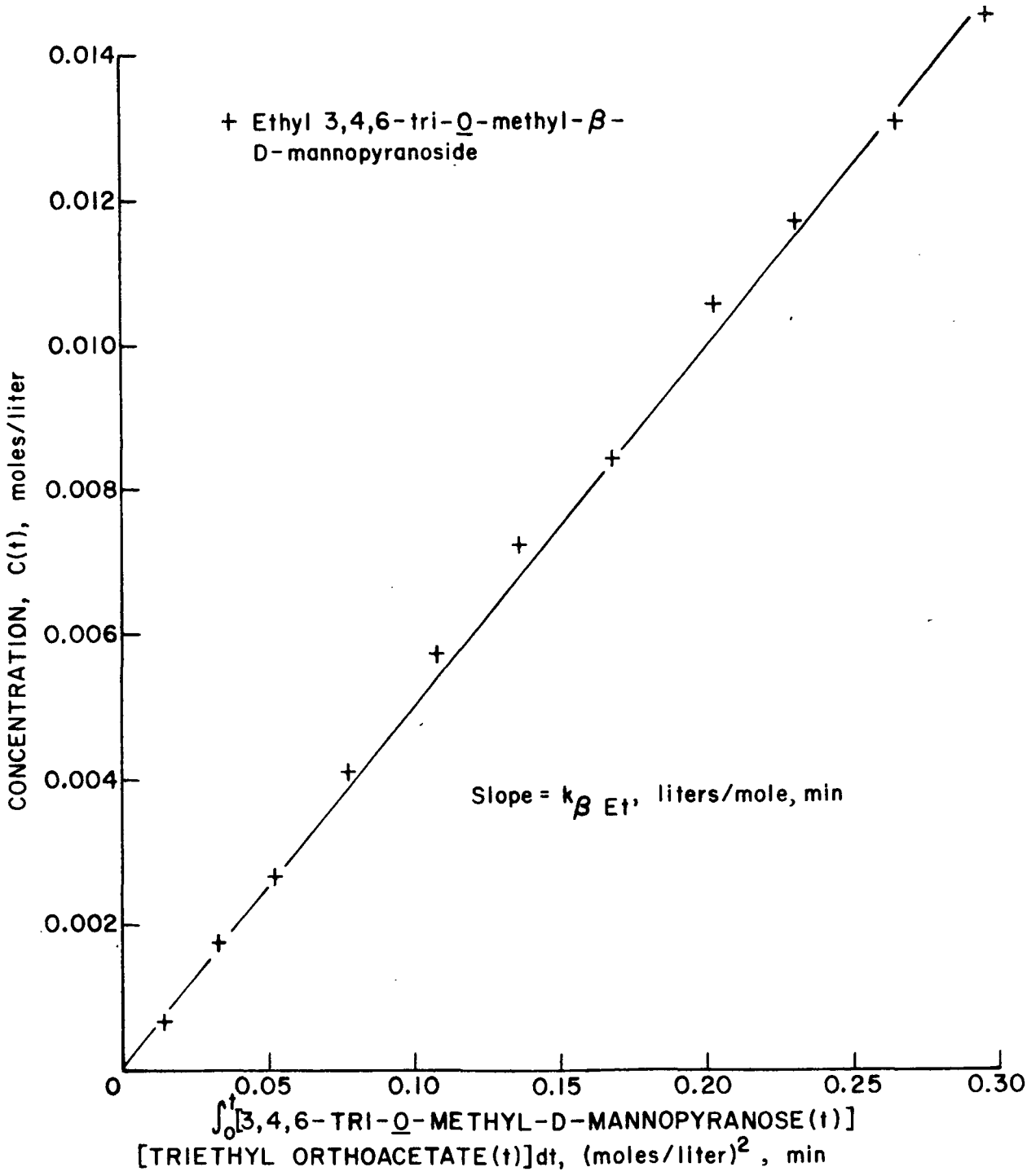


Figure 28. Plot Demonstrating that the Acid-Catalyzed Ethanolysis of 3,4,6-Tri-O-methyl-D-mannopyranose in the Presence of Triethyl Orthoacetate is First-Order in Both Reducing Sugar and Orthoester

APPENDIX VII

COMPUTER SIMULATION OF ETHANOLYSES

Computer simulations of 0.005N picric acid-catalyzed ethanolyses of 1,2-O-(1-ethoxyethylidene)-3,4,6-tri-O-methyl-β-D-mannopyranose and 3,4,6-tri-O-methyl-D-mannopyranose in the presence of triethyl orthoacetate were made based on the mathematical model given by Equations (8)-(14). A closed form solution of the simultaneous differential equations [Equations (8)-(14)] is difficult to obtain, but several techniques are available to solve the problem numerically (50). The method selected in this study involved the use of an IBM 1130 Continuous Systems Modeling Program (CSMP) adapted for an IBM 360 computer using Basic FORTRAN IV.

The 1130 CSMP may be classified as a special type of "general differential equation solver," in which the set of differential equations is specified by a special block-oriented language. The program solves the problem by means of a sorting algorithm which determines the order of computations and a numerical integration formula (second-order Runge-Kutta) which approximates the continuous integration process.

A block diagram showing the interconnections of elements required to implement the model (for mole fractions of carbohydrates) is given in Fig. 29. The values of the parameters are given in Table XXI. Minor additions to the block diagram given in Fig. 29 are necessary to simulate the ethyl acetate-plus-triethyl orthoacetate data, and polarimetric data. The additions to be made are based on the following equations:

$$(\text{Ethyl acetate + triethyl orthoacetate})_{\text{mole fraction}} =$$

$$(\text{ethyl 3,4,6-tri-}\underline{O}\text{-methyl-}\alpha\text{-D-mannopyranoside +}$$

$$\text{ethyl 3,4,6-tri-}\underline{O}\text{-methyl-}\beta\text{-D-mannopyranoside +}$$

$$\text{3,4,6-tri-}\underline{O}\text{-methyl-D-mannopyranose})_{\text{mole fraction}}, \quad (30)$$

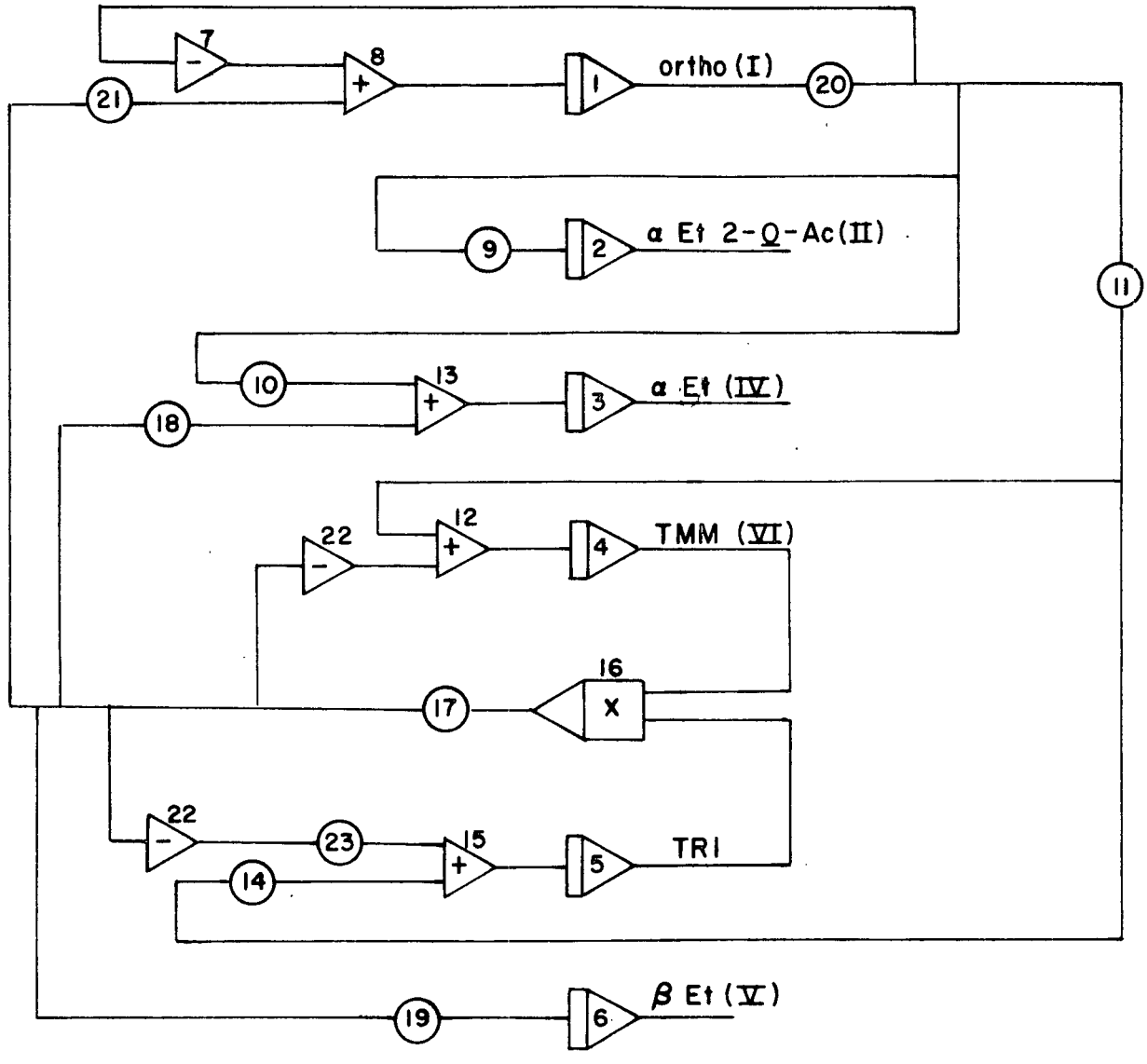
$$\alpha_m(t) = 0.01 \sum_i (\text{molecular wt. of i})(X_{i,t})\{[\alpha]_{Hg,i}\}, \quad (31)$$

where $\alpha_{\underline{m}}(\underline{t})$ = molar specific rotation

$X_{\underline{i},\underline{t}}$ = molar fraction of carbohydrate $\underline{i}$ at time $\underline{t}$

$[\alpha]_{Hg,\underline{i}}$ = specific rotation of carbohydrate $\underline{i}$ using 546-nm light.

The mole fractions of carbohydrates are given by the output of Blocks 1, 2, 3, 4, and 6 as shown in Fig. 29. The specific optical rotations of the carbohydrates are given in Table XIV.



Symbol	Description	Symbol	Description
	Integrator		Gain
+	Summer	x	Multiplier
−	Sign Inverter		

Figure 29. Block Diagram for the Computer Simulation of the Ethanolysis of 1,2-O-[1-(Exo-ethoxy)ethylidene]-3,4,6-tri-O-methyl-β-D-mannopyranose

TABLE XXI

VALUES OF PARAMETERS

Block Number		
20	$\sum_{i=1}^{3} \underline{k}_i$	0.0778 min^{-1}
9	$\underline{X}_{2,\infty}$	0.194
10	$\underline{X}_{3,\infty}$	0.160
11	$\underline{X}_{1,\infty}$	0.646
17	$\sum_{j=4}^{6} \underline{k}_j$	0.282 (L/mole min)
18	$\underline{X}_{5,\infty}$	0.343
19	$\underline{X}_{6,\infty}$	0.160
21	$\underline{X}_{4,\infty}$	0.497
1	Initial mole fraction (ortho)	a
4	Initial mole fraction (TMM)	a
5	Initial moles/liter (TRI)	a
14, 23	Moles/liter of mannose derivative	a

[a]Dependent upon reaction conditions used.

APPENDIX VIII

ESTIMATE OF THE PYRANOID RING CONFORMATION OF 3,4,6-TRI-O-ACETYL-1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-β-D-MANNOPYRANOSE

A 220-MHz NMR spectrum of 3,4,6-tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-β-D-mannopyranose is shown in Fig. 30. An enlargement of the spectrum between 800 and 1250 Hz is shown in Fig. 31. The coupling constants between protons on vicinal carbon atoms were determined. Analysis of the spectrum was based on simplified ABX analyses for H-4, H-3, H-2; H-5, H-4, H-3; and H-6a, H-6b, H-5 since in all of the systems $\Delta\nu_{AB} > 10$ Hz (43). The dihedral angles, which were estimated using the Karplus equations, are given in Table XXII.

TABLE XXII

ESTIMATE OF DIHEDRAL ANGLES OF 3,4,6-TRI-O-ACETYL-1,2-O-[1-(EXO-ETHOXY)ETHYLIDENE]-β-D-MANNOPYRANOSE

a,b	$J_{a,b}$ Hz	Dihedral Angle $\psi_{a,b}$ [a] (likely)	Dihedral Angle $\psi_{a,b}$ [a] (other)
1,2	2.5	55°	123°
2,3	4.0	45°	131°
3,4	10.0	180°	0°
4,5	9.75	180°	0°

[a] Estimated using the following equations (51):

$$J_{a,b} = 8.5 \cos^2\phi - 0.28 \quad 0° \leq 90°.$$

$$J_{a,b} = 9.5 \cos^2\phi - 0.28 \quad 90° \leq 180°.$$

The most likely values of the dihedral angles suggest that the pyranoid ring exists in a slightly distorted $^4C_1$ conformation (see page 78).

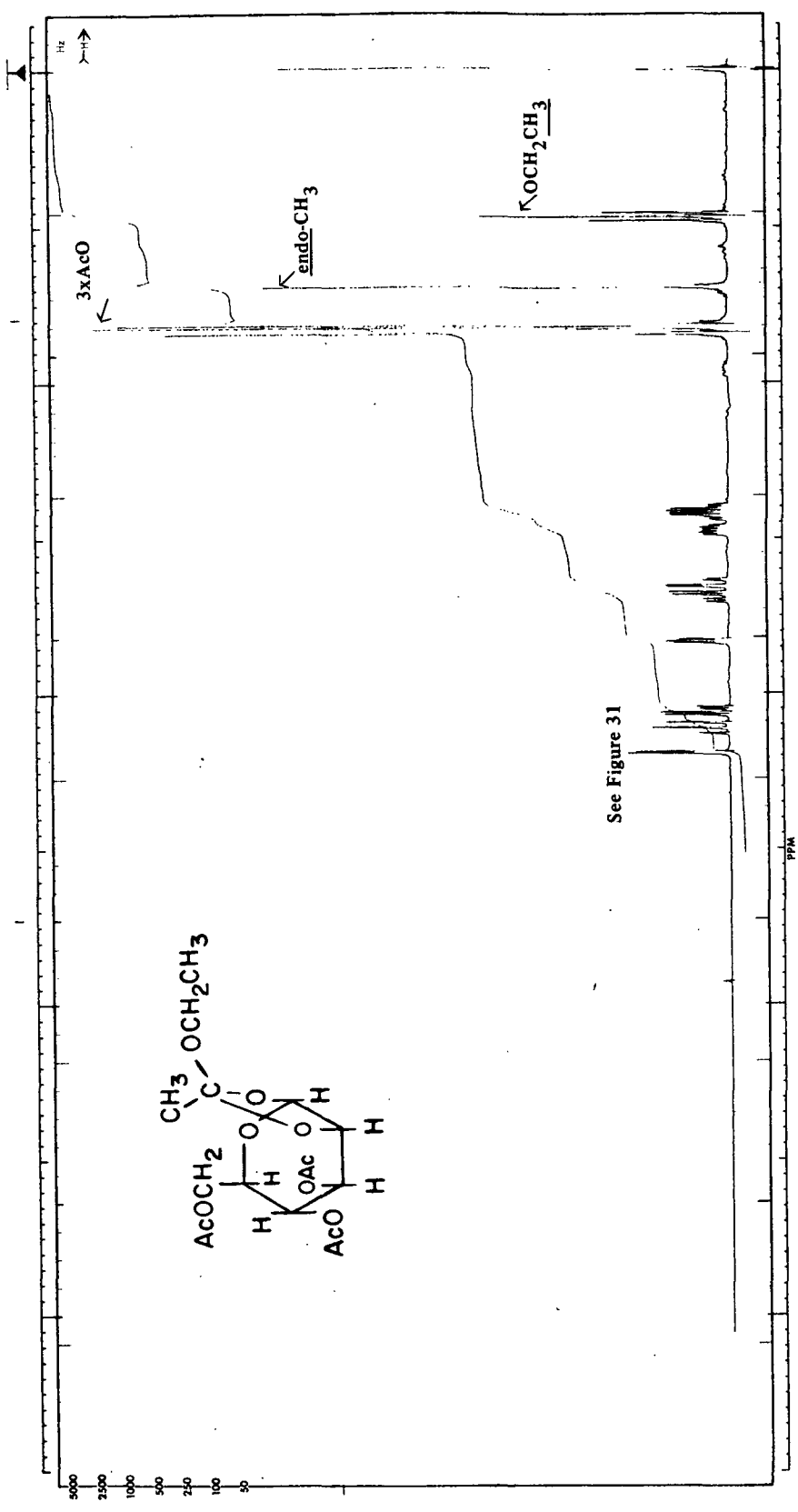


Figure 30. 220-MHz NMR Spectrum of 3,4,6-Tri-O-acetyl-1,2-O-[1-(exo-ethoxy)ethylidene]-β-D-mannopyranose